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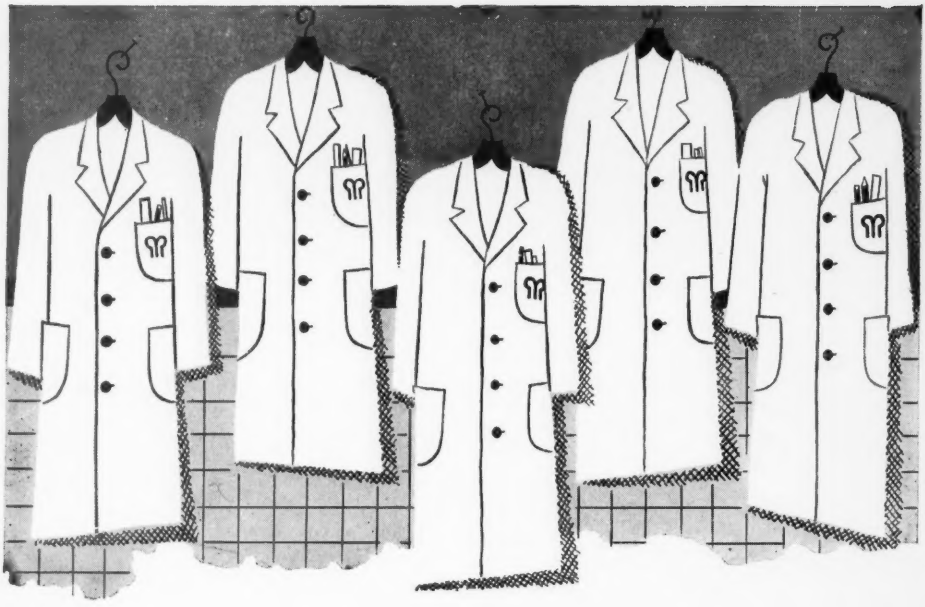

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OBSERVATIONS ON THE METABOLIC AND ANTIARTHRITIC EFFECTS OF ACTH AND CORTISONE IN DIABETICS

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IN THE absence of knowledge of the mechanism by which cortisone or adrenocorticotropic hormone (ACTH) influences rheumatoid arthritis (1), it seemed worthwhile to examine the relation of this antiarthritic action to the other known effects of the adrenal cortex. For example, desoxycorticosterone is about 50 times as effective as cortisone in sodium retention (2), yet desoxycorticosterone is ineffective in arthritis. Rheumatoid arthritis is not commonly present in Addison's disease and no demonstrable disturbance of electrolyte regulation occurs in arthritis. The relatively small changes in electrolyte excretion at certain periods of successful treatment with cortisone (3) may be added to these observations, all of which suggest that the antiarthritic action of the adrenal cortex is distinct from its function as a regulator of electrolytes. In like manner,

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the failure of sex hormones to influence arthritis, in our experience, and the favorable response of arthritis to cortisone with or without an increased excretion of 17-ketosteroids (3) indicate that the sex hormones of the adrenal cortex are probably not responsible for the influence of the adrenal hormones in arthritis.

Because the 11-oxysteroids have the greatest if not the only antirheumatic activity and because these steroids are the most potent in their influence on protein and carbohydrate metabolism, an attempt has been made to observe the relation between the metabolic effects of the adrenal cortical steroids and their antirheumatic function. To do this, patients with diabetes and arthritis were examined for the effects on the arthritis of (a) the adrenal cortical response which follows marked reduction of insulin dosage (presumably the same as the response seen when the gland is stimulated with ACTH, although there may be a great difference between the degree of ACTH effect which follows the withdrawal of insulin and that which follows the administration of an antirheumatic dose of ACTH), and (b) ACTH or cortisone therapy under varying degrees of control of the diabetes. This does not imply that the metabolic actions of cortisone are suppressed by insulin; it does mean that certain manifestations of these effects, such as glycosuria and ketonuria, are controlled. In the absence of knowledge of the underlying biochemical processes, it is clear that such gross clinical findings will not justify fundamental conclusions. However, the results in these somewhat unusual patients are in agreement with what has been observed by others who have studied adrenal physiology and the antirheumatic activity of the adrenal cortex.

METHODS

For this study, 3 patients were chosen who had active rheumatoid arthritis and severe diabetes mellitus. Under hospital care, gross changes in the manifestations of diabetes were induced by varying the insulin dosage before and during treatment with ACTH or cortisone. In each patient the protein, carbohydrate and fat content of the diet was determined by weighing. The diet prescribed for D.R. contained 80 Gm. of protein, 70 Gm. of fat, and 150 Gm. of carbohydrate per day. The diets of G.M. and R.G. are shown in the figures. There was no regulation of the intake of sodium and potassium in D.R. or G.M. but the diet of R.G. contained 35 to 40 mEq. of sodium and 45 to 50 mEq. of potassium per day by analysis.

Analyses were made for urinary glucose (4). Sodium and potassium were determined by means of a Barclay internal standard flame photometer, and nitrogen by the Kjeldahl method.

Following control periods, and in 2 cases after periods of decreased insulin dosage, treatment was given at the dosage levels shown in the

figures. The doses of ACTH[1] shown in the figures indicate the milligrams of the standard contained in the daily dose. Doses of 100 mg. or more per day were given as divided doses, intramuscularly, at six-hour intervals. Smaller doses were given at eight-hour or twelve-hour intervals.

The ACTH showed no local or systemic toxic effects in the patients and its clinical potency has been excellent as observed not only in these studies but in the subsequent maintenance of relief of arthritis with smaller doses. Cortisone (Merck) was administered once daily as a microcrystalline suspension in saline (1).

RESULTS

The results are shown graphically in Figures 1 through 6.

D.R., the first patient, was a woman of 43 who had been a severe diabetic for seven years. Nine months before her admission rheumatoid arthritis had developed, involving the hands, shoulders, ankles and neck. Figures 1 and 2 show the principal studies. After a few days, not charted, in which her insulin requirement was established, insulin was greatly reduced. This resulted in marked glycocuria and acetonuria and on the morning of the fourth day of this period a mild acidosis was evident with a plasma CO_2 of 21 volumes per cent. The acidosis was easily corrected by 140 units of insulin. On this day, the eosinophil count was strikingly lowered and this was confirmed by a second count done later in the day. This response of the eosinophils agrees with the results of McArthur and Butler (personal communication) who found a fall in the circulating eosinophils in experimental diabetes when insulin was withdrawn. The patient experienced slight thirst, nausea and weakness a few hours before the acidosis was treated. Although the increased excretion of glucose and nitrogen and the eosinopenia are interpreted as indicating considerable activity of the adrenal cortex, there was no clearly defined effect on the arthritis. It is, of course, possible that a more prolonged acidosis would have affected the arthritis but the patient's welfare forbade this.

The control period which followed the reduction of insulin and the control period after treatment should be considered together. They suggest the labile type of diabetes which this patient had. It is also possible that regulation of the diabetes was more difficult after the withdrawal of insulin and that it was better regulated after treatment because of the short period of adrenal insufficiency which has been described on stopping treatment (5). After the first control period, cortisone was given. During this treatment period insulin was increased on the second day but this still permitted an increase in glycosuria and the appearance of ketonuria for the first two days. Thereafter the glucose and nitrogen excretion were within the range of values of the control period. The response of the arthritis to cortisone was excellent and need not be described in detail except to note that it began at forty-eight hours or during the increased glycosuria and progressed satisfactorily for the rest of this period, during controlled glycosuria. The seven days of cortisone treat-

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[1] We are indebted to Dr. K. W. Thompson, Organon, Inc., Orange, N. J., for the purified adrenocorticotropic hormone used in these studies. Its biologic activity was assayed to agree with the Armour L A-1-A standard, *i.e.*, a single intravenous injection of 0.004 mg. produces consistently a 20 to 30 per cent decrease in adrenal ascorbic acid content in the hypophysectomized rat.

ment was terminated by two days of ACTH therapy for the purpose of avoiding the prompt relapse which often occurs after a short course of cortisone. After these studies the arthritic symptoms were controlled by 25 mg. of ACTH taken every other day. Symptoms recurred five days after the last dose.

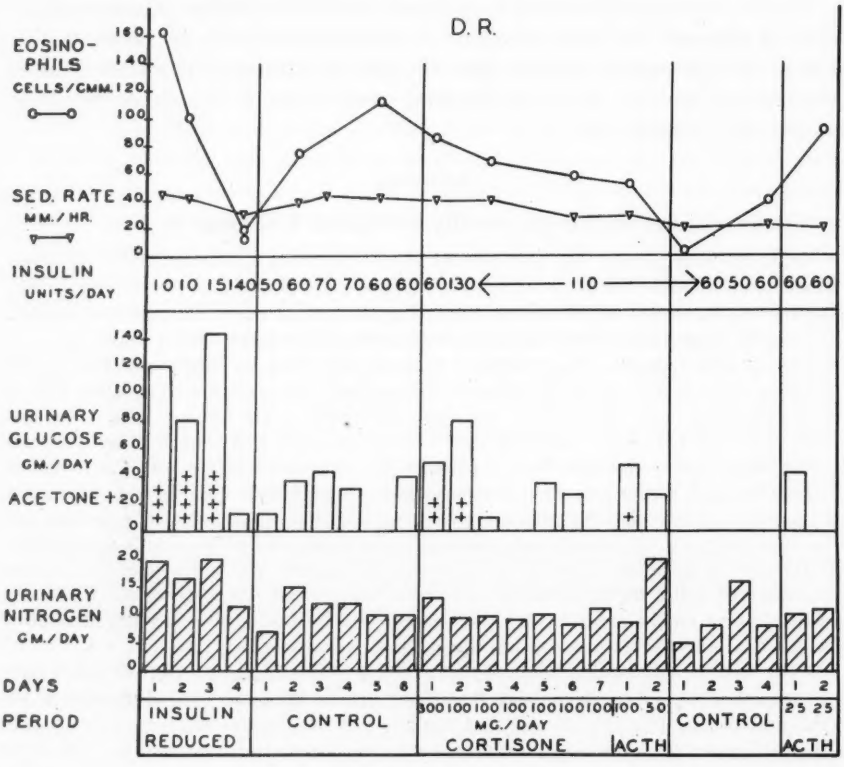

FIGURE 1

In D.R. adrenal cortical function, sufficient to permit an increase in glycosuria after the reduction of insulin, failed to influence the arthritis in three days. This may be contrasted with the marked improvement subsequently produced within two days when cortisone was given. Cortisone appeared to produce ketonuria at a lower level of glycosuria than did the withdrawal of insulin. The good effects of cortisone began while the signs of diabetes were increased, *i.e.*, in the first two days, but favorable progress continued when insulin was increased enough to restore the diabetes to the control level. Consequently, in Table 1, this patient has been listed both as a response to cortisone during increased glycosuria because of the first two days (Group 3) and as a response when there was no increased glycosuria because of her progress in the last days of treatment (Group 4).

Figure 2 shows the weight curve and the urinary excretion of sodium and potassium. The loss of weight when insulin was decreased, the marked gain in weight during treatment and the loss of weight after the treatment period, have been described by others. These changes appear to reflect particularly the alterations in the excretion of sodium. The sodium and potassium loss in uncontrolled diabetes is an old story. It is noteworthy

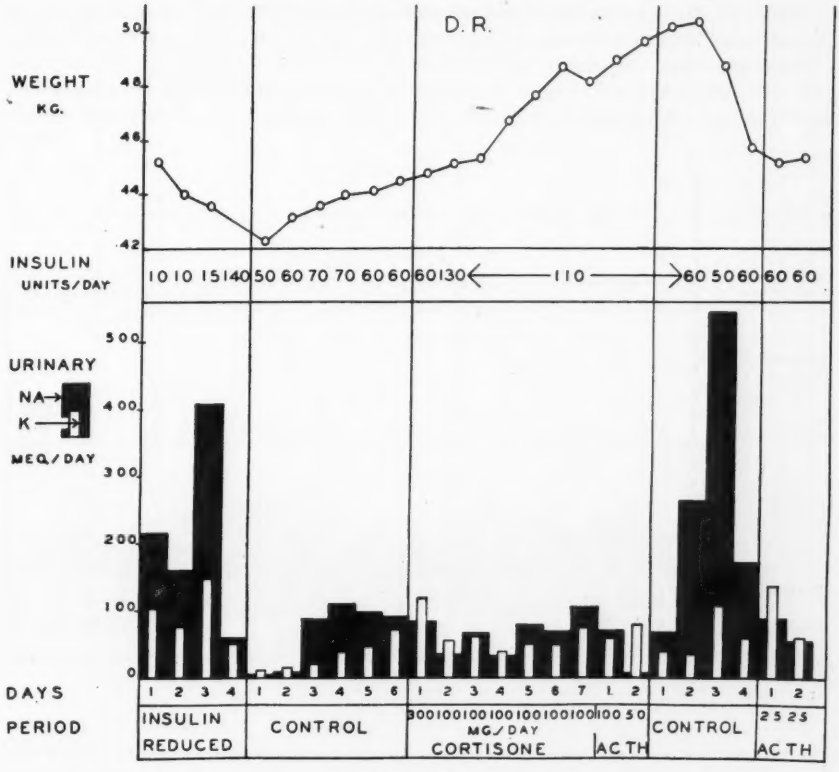

FIGURE 2

that the sodium retention during the first two days of the subsequent control period was greater than the sodium retention at any time under cortisone. This provides an illustration of the apparent dissociation of sodium retention and antirheumatic effect, for the patient's arthritis was unchanged during this control period. It will be noted that the sodium retention after reduced insulin dosage accomplished the restoration of a deficiency in sodium, whereas the lesser retention of sodium during cortisone therapy occurred when the patient was supposedly in good sodium balance. Although the intakes of sodium and potassium were not measured, the same diet was taken and the patient was unaware of changes in salt appetite at this time. Later during cortisone and ACTH treatment she reported a slightly increased desire for salt. The marked diuresis, weight loss

and sodium excretion of the second control period are in accord with the reports of others.

G.M., the second patient, was a woman 42 years old who had severe diabetes of eighteen years' duration. Rheumatoid arthritis involving particularly the hands, wrists, and ankles was of two years' duration, during which early scleroderma of the hands, feet and face had developed. Figure 3 outlines the changes in her diabetes during the study. The diabetes was more stable and less severe than that of D.R., but a marked glycosuria and moderate ketonuria were produced on the third day of the period on reduced insulin. Nitrogen excretion was slightly increased on the third day. Although she thought her pain was slightly less, the changes in mobility and swelling of the joints were negligible. After a second control period, treatment with ACTH was instituted. This caused a strik-

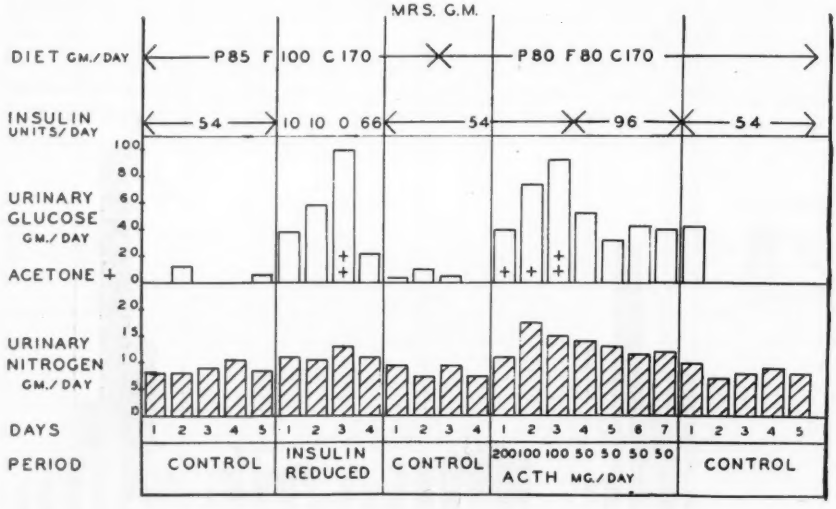

FIGURE 3

ing improvement in the arthritis, and also in the early scleroderma, beginning within twenty-four hours. Her insulin dosage during ACTH therapy was not increased at first. On this regimen ACTH caused glycosuria and ketonuria as severe as on the day when she had no insulin. The nitrogen excretion increased markedly from about 10 Gm. per day to 17 Gm. on the second day of treatment. The most significant changes in her collagen disease occurred during the first three days when the diabetes was made worse. The improvement continued when additional insulin was given to improve the control of the diabetes. Although the diabetes was not fully restored to the control level of glycosuria, this patient is also listed in Table 1 as one who improved with and without increased glycosuria.

Figure 4 shows the changes in weight and electrolyte excretion. There was only a slight increase in sodium output when insulin was reduced and no demonstrable sodium retention occurred in the second control period. The administration of ACTH caused striking sodium retention with little or no change in potassium excretion after the first

day of the period. The response to the cessation of ACTH resembles that of the first patient.

R.G., the third patient, was a 37-year-old man who had had diabetes for five years and rheumatoid arthritis involving especially the hands, feet and ankles for two years. His diabetes was severe, somewhat labile and had been difficult to manage before admission. In the hospital he was fairly well regulated on a diet of 90 Gm. of protein, 90 Gm. of fat, and 220 Gm. of carbohydrate daily with 100 units of insulin daily. On this

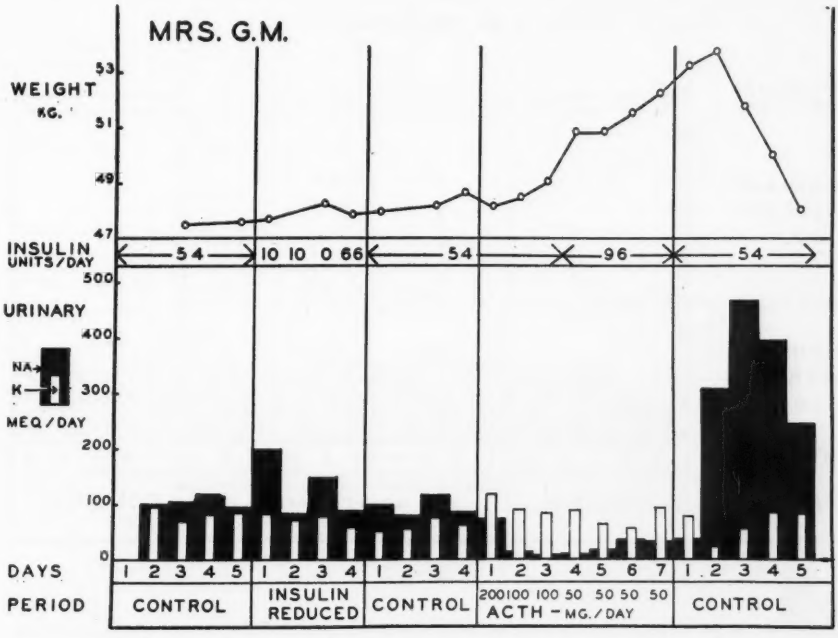

FIGURE 4

regimen he had a moderate, irregular glycosuria (Fig. 5). The omission of one dose of insulin was probably responsible for the high glycosuria of the last two days of the first control period. When cortisone was administered the insulin dosage was not increased. In contrast to the other patients he showed only a moderate increase in glycosuria, a moderate increase in nitrogen excretion and only traces of acetonuria. Since the average glycosuria was 16 Gm. per day in the control periods compared to 56 Gm. daily while under the influence of cortisone and the average nitrogen excretion rose from 11.4 to 13.2 Gm. per day, he has been placed in group 3 in the table. One factor in these irregular results was his activity. For example, on the fourth day of the cortisone period the slight glycosuria is attributed to the fact that he could not sleep and worked on the ward most of the night. It may be noted that the first 2 patients had to have their insulin increased to approximately 100 units daily to offset, to some extent, the diabetogenic influence of ACTH or cortisone. It may be that the mild or relative insulin resistance of this patient

was due to the arthritic process and that the alleviation of this disease permitted him tolerate the cortisone without increasing the insulin.

His arthritis responded to cortisone in a striking manner and the relief of pain, stiffness, and swelling was accompanied by a fall of the internal temperature of the ankle joint to normal (6). Incidentally, he was the first patient in our experience to have almost complete disappearance of rheumatoid nodules (7).

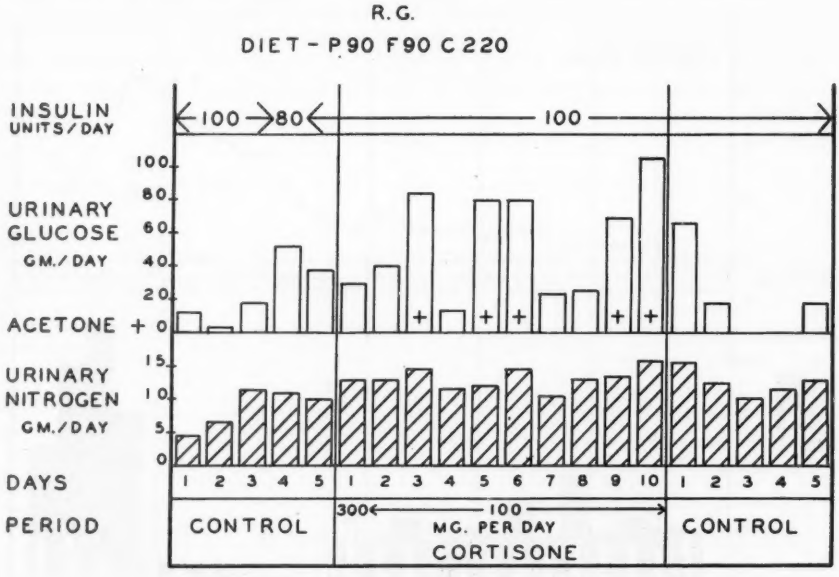

FIGURE 5

Figure 6 shows that in response to cortisone the eosinophil count fell. The sedimentation rate which was not greatly elevated was unaltered and there was no increase in weight. Cortisone appeared to delay a loss of weight by means of an initial sodium retention. From the fifth to the ninth days of treatment sodium excretion was about at the control level, apparently due to the "rebound despite continued administration" of the hormone (5). This was seen only in this patient on a fixed sodium intake and it will be noted that when treatment was discontinued the sodium diuresis was about half that of the other 2 patients. This may be individual variation or may indicate the degree to which the appetite for salt influenced the response of D.R. and G.M. to these procedures.

COMMENT

The summary in Table 1 includes two sets of observations in addition to the data which have been presented. The first observation is that the majority of arthritic patients respond to cortisone or ACTH without glycosuria or major deviations of the blood sugar (3). This is indicated in Group 1 which is based on the experience in the University of Pennsylvania

Hospital to date. The second observation is that the administration of 100 units of insulin daily during the first few days of cortisone or ACTH therapy does not alter the effect on the arthritis in our experience (Group 2), a result which agrees with some unreported experiences of others. Relief of arthritis may take place in the presence of a greatly increased excretion of glucose and nitrogen (Group 3) or without increased glycosuria

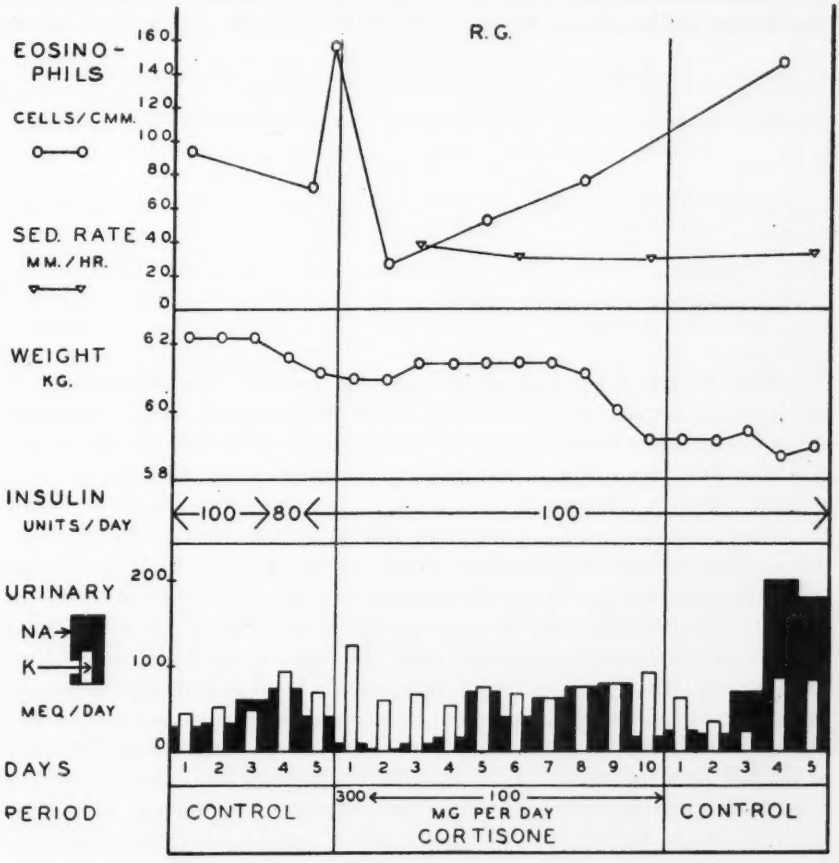

FIGURE 6

(Groups 1, 2, 4). Reduction of insulin dosage without adrenal therapy results in an increase in the signs of diabetes and in eosinopenia, which in turn presumably depend upon increased adrenal cortical activity. In spite of these manifestations of an adrenal response which is of the 11-oxysteroid type no definite benefit to the arthritis was observed (Group 5).

Cortisone and ACTH have been given to diabetic patients with Addison's disease, but we know of only 1 example in the literature of its use in diabetes and arthritis. This patient, reported by Boland and Headley (7), required only 10 units of insulin prior to cortisone. During treatment with cortisone "30 to 50 units of insulin were required to control the diabetes." It seems that this patient could be added to group 4 (Table 1).

Throughout this report the assumption has been made that a conspicuous increase in the urinary excretion of glucose, nitrogen and ketone bodies

TABLE 1. CHANGES IN DIABETES AND ARTHRITIS UNDER VARIOUS CONDITIONS

Group No.	Arthritic patients	No. of patients	Insulin given	ACTH or cortisone	Glycosuria increased	Arthritis improved
1	nondiabetic	29	none	yes	no	yes
2	nondiabetic	2	100 units	yes	no	yes
3	diabetic	3	none extra	yes	yes	yes
4	diabetic	2	extra	yes	no	yes
5	diabetic	2	less	no	yes	no

indicates increased activity of the adrenal cortex. This assumption is based on the striking modification of these diabetic phenomena when the adrenal glands are removed from the depancreatized animal (8). Secondly, it was at first impossible to increase the severity of the diabetes of such animals with the adrenal cortical extracts then available. However, when an adrenal remnant small enough to result in an ameliorated diabetes was left in depancreatized animals, adrenal cortical extract in large dosage enhanced the diabetes (9). A similar response has since been observed in patients with diabetes and Addison's disease (10). Thirdly, at certain fixed levels of adrenal cortical therapy, some response to the withdrawal of insulin occurs (10). The question of an adequate level of secretion versus an increased rate of secretion of adrenal cortical hormones cannot be answered dogmatically. Finally, the modern criteria of adrenal cortical activity, such as the fall in eosinophils and the excretion of urinary corticosteroids, have been added to the picture by McArthur, Sprague and Mason (11). They showed that in diabetic acidosis the "rate of corticosteroid excretion was from two to eight times as rapid as the rate after recovery." In one of their patients insulin was withdrawn for fifty-four hours. In the last six hours of this period the eosinophil count fell to a very low level but even then the corticosteroid excretion was not significantly increased. In the absence of corticosteroid determinations in our patients, one might perhaps infer from the report of McArthur, Sprague and Mason (11) that our patients

would have had little significant rise in corticosteroid excretion. The increase in adrenal cortical secretion may well have been small. If this is so, the basal rate of secretion must have been adequate, in order that the manifestations of diabetes be increased when the dose of insulin was reduced. Whether one regards the adrenal cortical activity as increased or merely as ample to aggravate the signs of diabetes, the arthritis was not influenced at this level of adrenal function. Even if this failure to affect the arthritis is a matter of the amount of secretion, the possibility that there is a dissociation between the "diabetogenic" and the antiarthritic effects of the adrenal cortex should be entertained. Such a concept must be highly tentative in view of the crude measurements which lead to its suggestion.

SUMMARY

Three patients with severe diabetes and active rheumatoid arthritis were studied under various regimens. Following the reduction of insulin and the consequent increase in the urinary excretion of glucose, nitrogen and ketones, no effect on the arthritis was observed. When treated with ACTH or cortisone, marked improvement in the arthritis occurred irrespective of whether the manifestations of diabetes were exaggerated or controlled. These observations, which supplement the studies of others in nondiabetics, suggest that the effect of the adrenal hormones in rheumatoid arthritis is not closely correlated with the gross manifestations of their metabolic functions and therefore may be independent of these activities.

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THE EFFECT OF ADRENOCORTICOTROPIN AND CORTISONE ON THYROID FUNCTION: THYROID-ADRENOCORTICAL INTERRELATIONSHIPS*†

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INTRODUCTION

THE thyroid-adrenal interrelationship has interested medical investigators for over fifty years. A protective action of adrenocortical steroids against thyroid intoxication has been shown repeatedly (1–11). The experiments of Marine and Baumann (12, 13), which were confirmed by others (14–16), demonstrated an apparently increased activity of the thyroid in the presence of partial adrenal cortical insufficiency. The lymphoid and thymic hyperplasia in hyperthyroidism, as well as in adrenal cortical insufficiency (2, 17–20), the involution of these tissues by adrenal cortical steroids (21–23), and the inactivation of thyrotropic hormone by the same tissue (24) all point to a close physiologic relationship between the thyroid and adrenal glands.

A depression of thyroid function in animals and in man has been reported following stress, the administration of cortisone acetate (11-dehydro-17-hydroxycorticosterone acetate), ACTH (adrenocorticotropic hormone) and epinephrine (25–29). In patients with Addison's disease, the thyroid depression induced by cortisone was preceded by an initial stimu-

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This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1951.

lation. The availability of ACTH, TSH and cortisone for clinical use and the improvement in the techniques of measuring thyroid and adrenal cortical function have stimulated further work on the thyroid-adrenal relationship.

An attempt has been made in the present studies to define the effect of varying levels of adrenal cortical activity on thyroid function, both at the thyroid and at the peripheral levels, using the technique of I^{131} uptake, the serum protein-bound iodine and the basal metabolic rate as indicators of change in thyroid activity. At the same time an attempt has been made to determine the effect of varying levels of thyroid function on the adrenal cortical response to the administration of ACTH.

METHODS

The present studies were carried out on patients and subjects under dietary control on the metabolic service of the Peter Bent Brigham Hospital. The radioactive iodine (I^{131}) uptake by the thyroid gland was determined, using the technique described by Astwood and Stanley (30). Following an initial oral dose of 50–100 microcuries of I^{131} given in the fasting state, the rate of uptake was determined at one-half to one-hour intervals by direct counts over the thyroid gland for a period of four to eight hours. By plotting the increase in counts per second against the square root of time in minutes, a straight line is obtained. A numerical expression of the slope of this line, the accumulation gradient (G), can be calculated by dividing the increase in counts per second over a given time interval by the square root of this time in minutes. The normal accumulation gradient as determined in this laboratory ranges from 1.0 to 10, with a mean of 3.7; hyperthyroid patients usually have a gradient greater than 10 and hypothyroid patients usually have a gradient less than 1. The gradient in the same person usually varies little over a period of several weeks and, therefore, if any decided change occurs it can be used in conjunction with other findings to indicate a significant change in actual thyroid activity. The majority of the serum protein-bound iodine determinations were done by the method of Barker (31), as modified by Carr and coworkers (32) in the latter's laboratory. Normal values range from 3.5–8.0 gamma per cent. Serial determinations of the serum protein-bound iodine by this method have been shown to remain quite constant in healthy subjects over a period of four to seven weeks, with variations of between 0.3–1.1 gamma per cent (33). The basal metabolic rate in most cases was determined by the Benedict-Roth technique. In a few instances the basal oxygen consumption was estimated by determining the nonprotein respiratory quotient obtained by the use of a Tissot spirometer. The chemical and hematologic methods

were those previously employed in metabolic studies on the effect of ACTH by Forsham *et al.* (23).

MATERIALS

Cortisone acetate (compound E acetate) was administered in three forms: 1) intramuscularly, as a supersaturated solution in sesame oil containing 10 mg. of hormone per ml.[1]; 2) intramuscularly, as a microcrystalline suspension in saline, containing 25 mg. per ml.; and 3) subcutaneously, as cylindrical pellets, 3 mm. in diameter, weighing 50–200 mg. each,[1] which provided a total daily dose of hormone of approximately 1 per cent of the pellet weight.[2] Purified adrenocorticotropin[3] (ACTH) prepared by the Armour Laboratories from hog pituitary glands was used as a direct adrenal cortical stimulant (23). The ACTH was administered intramuscularly as a saline solution containing 5–25 mg. per ml. Twenty to thirty-milligram doses of thyrotropin[3] (TSH) in a saline solution, were administered intramuscularly as a single dose or at six-hour intervals. Desiccated thyroid substance was given orally in dosages which refer to the U.S.P. standard preparations. Radioactive[4] iodine, I^{131}, was obtained from the Atomic Energy Commission,[5] Oak Ridge, Tennessee, and was administered orally, in 50–100 microcurie doses, carrier-free and dissolved in water.

OBSERVATIONS

Normal thyroid and adrenal cortical function

ACTH given to 10 subjects with normal thyroid and adrenal cortical function for periods ranging from eight to thirty-three days led to a prompt adrenal cortical response, as measured by a decrease in the circulating eosinophils and a rise in urinary 17-ketosteroid excretion (23). At the same time, there was a 77 to 100 per cent progressive decrease in the I^{131} accumulation gradient. In 2 of these subjects there was no demonstrable uptake of I^{131} at the end of ACTH administration (Figs. 1 and 2).

Independently of the change in accumulation gradient, the peak of I^{131} uptake following adrenal cortical stimulation rarely reached the initial level, in terms of counts per second, obtained prior to ACTH administra-

We are indebted as follows for the materials used in this study:

[1] To Dr. A. Gibson of Merck and Company for a portion of the cortisone.

[2] To Dr. E. Oppenheimer of Ciba Pharmaceutical Products for the desoxycorticosterone acetate pellets.

[3] To Dr. John R. Mote of the Armour Laboratories for the ACTH and TSH.

[4] To Dr. A. K. Solomon of the Biophysics Department, Harvard Medical School, for handling the radioactive iodine.

[5] To the United States Atomic Energy Commission for the I^{131}.

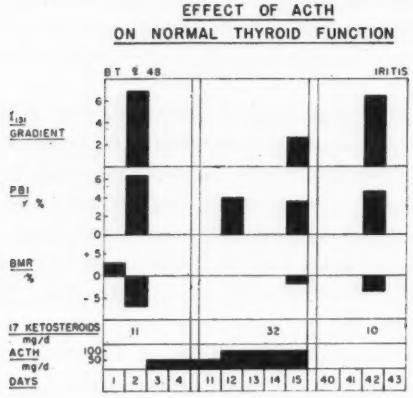

FIGURE 1

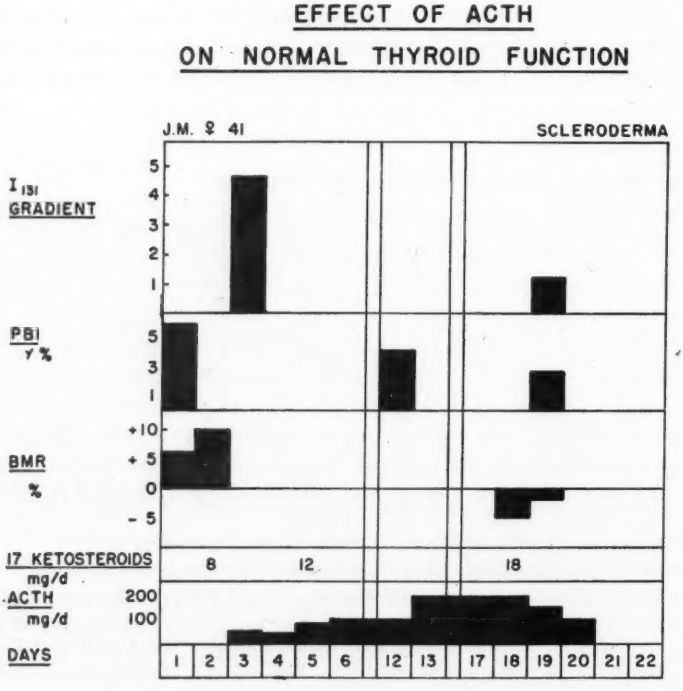

FIGURE 2

tion. One might refer to this peak of I^{131} accumulation as the "iodine space." The decrease in the "iodine space" occurred within one to four hours following the administration of ACTH and usually became more marked as the ACTH was continued. The exact significance of this decrease in "iodine space" remains to be evaluated. Following withdrawal of ACTH, there was a prompt return of the I^{131} accumulation gradient and "iodine space" either to, or above the initial level.

Serum protein-bound iodine levels, determined in 9 subjects, were found to be decreased in 6, slightly increased in 2 and unchanged in 1 (Figs. 1 and 2).

Basal metabolic rates remained unchanged in 3 subjects, decreased slightly in 2 and increased slightly in 2 others.

Serum cholesterol levels were decreased slightly in 2 subjects in whom determinations were made.

Immediately following discontinuance of the ACTH there was a return of the I^{131} accumulation gradient and serum protein-bound iodine level toward or above the control value and a rebound decrease in basal metabolic rate in most subjects (Figs. 1 and 2).

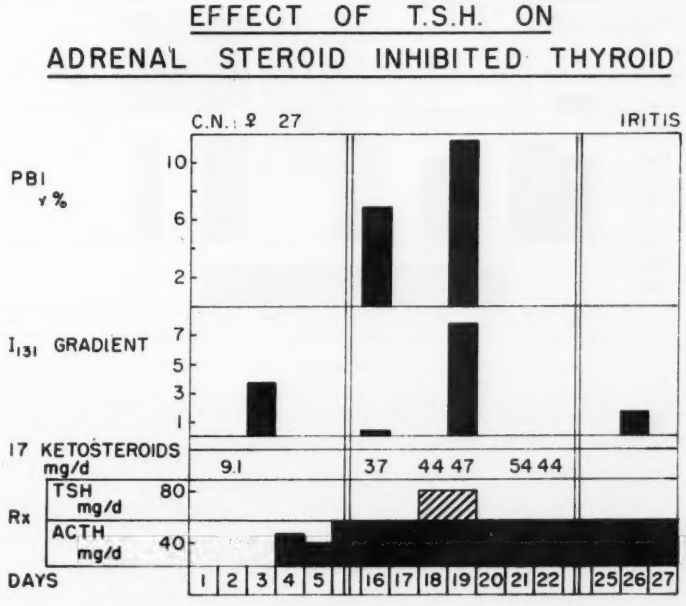

FIGURE 3

Eighty mg. of thyroid-stimulating hormone (*TSH*)[6] was administered daily for two days to a 27-year-old female whose I^{131} gradient had decreased from 3.7 to 0.4 following fifteen days' therapy with 80 mg. of ACTH per day. Following TSH therapy, the I^{131} gradient increased to 7.7 and the serum protein-bound iodine from 6.8 to 11.6 gamma per cent, although the adrenal cortex continued to be maintained at a high level of activity with ACTH (Fig. 3).

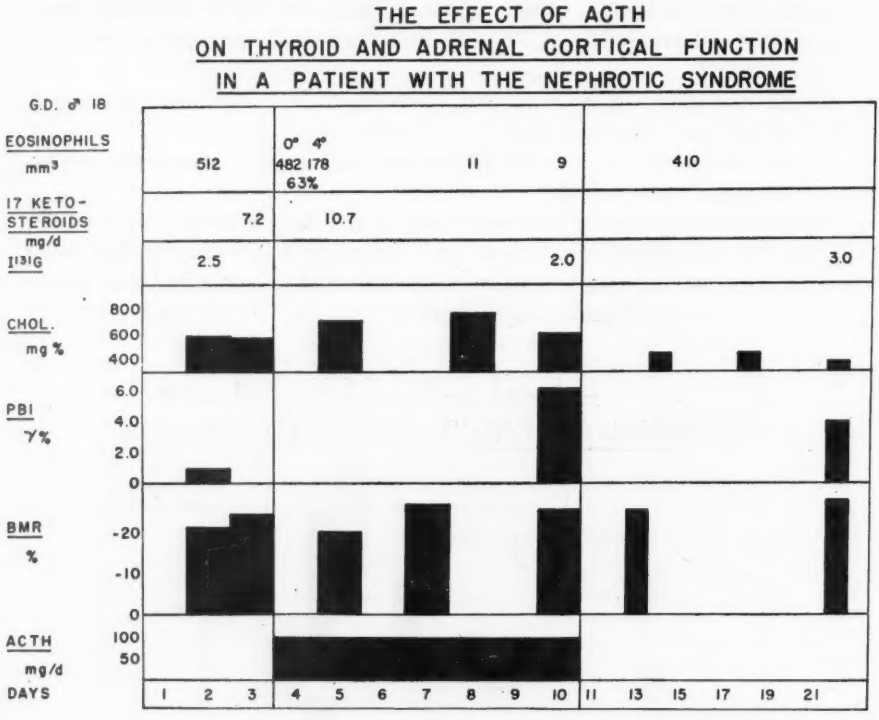

FIGURE 4

Certain patients with nephrosis behaved differently. ACTH was administered in doses of 80 to 160 mg. per day for seven to twenty days to 4 patients, and *cortisone* in doses of 100 mg. a day for ten days to 1 patient, with the nephrotic syndrome. The initial I^{131} accumulation gradient was within normal limits in all patients: it increased in 2 and remained unchanged in the others during therapy. The initial serum protein-bound iodine was decreased in 2, was normal in 2, and increased in 1 patient. In

[6] The TSH used in these studies assayed at 3.8 Evans chick units per milligram, according to the data furnished by the Armour Laboratories.

2 patients, 1 treated with ACTH and 1 with cortisone, in whom there was an initially low serum protein-bound iodine level, there was a sustained *rise* following adrenal steroid therapy (Fig. 4). In 1 patient in whom there was an initially normal serum protein-bound iodine level, there was an early increase and a subsequent decrease following prolonged ACTH therapy. In 2 patients with initially normal serum protein-bound iodine levels, there was a decrease during ACTH therapy comparable to that seen in normal subjects. The initial basal metabolic rates were decreased in all patients. They either remained unchanged or decreased slightly. The urine protein-

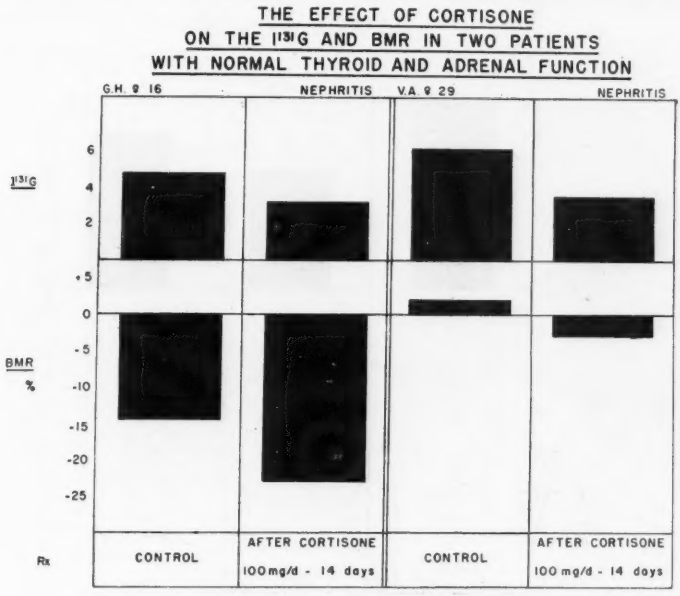

FIG. 5. The basal metabolic rates shown represent the mean of two or more determinations.

bound iodine remained constant at approximately 1.5 to 2.0 gamma per cent in 1 patient in whom there was a marked rise in serum protein-bound iodine during ACTH therapy.

Cortisone acetate administered to 4 subjects for fourteen days induced changes similar to those observed with ACTH. There was a decrease in I^{131} accumulation gradient and "iodine space" in all; serum protein-bound iodine levels were slightly increased in 2 subjects, and decreased in 2 others; basal metabolic rates decreased slightly in 1, remained unchanged in another, and increased in 2 others (Figs. 5, 6); serum cholesterol decreased slightly in the one subject in whom it was determined. Following

discontinuance of cortisone the changes were similar to those observed following discontinuance of ACTH, although delayed in their appearance, since the activity of cortisone may persist for three to five days following the last injection.

Summary: It would appear that both ACTH and cortisone administered to subjects with normal thyroid and adrenal function consistently induce a depression of I^{131} accumulation gradient. In 8 of 13 subjects, a decrease in the serum protein-bound iodine level occurred. At a time when both the

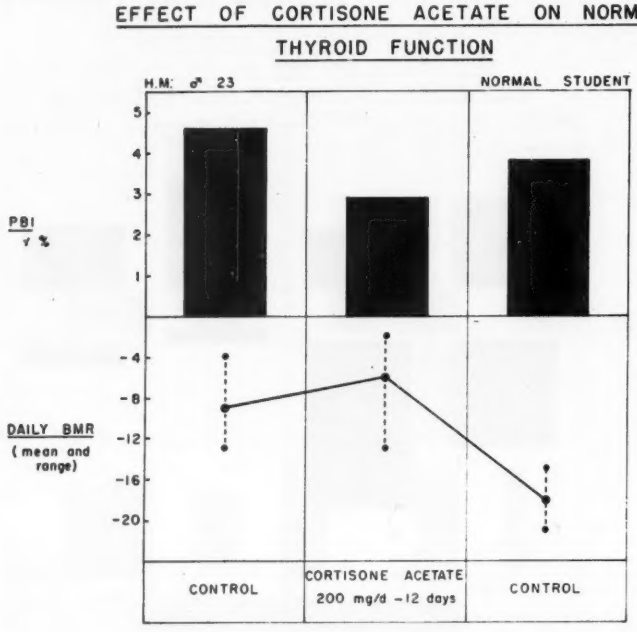

FIGURE 6

I^{131} accumulation gradient and the serum protein-bound iodine were slightly to moderately decreased, the basal metabolic rate either increased slightly or remained unchanged. As the decrease in serum protein-bound iodine and I^{131} accumulation gradient became more marked, the basal metabolic rate also decreased. Serum cholesterol levels tended to be decreased when measured.

Following discontinuance of hormone, there tended to be a return of I^{131} accumulation gradient and the serum protein-bound iodine level toward or above the control value and a rebound decrease in basal metabolic rate.

Among patients with the nephrotic syndrome some, especially those with an initially low serum protein-bound iodine, show an anomalous response

to ACTH or to cortisone in that there is a rise in protein-bound iodine and accumulation gradient rather than a fall, during administration of these hormones.

Administered TSH proved capable of stimulating a thyroid response following inhibition by, and in the presence of, a high level of circulating adrenal steroids.

Addison's disease

From earlier work in patients with untreated or *desoxycorticosterone*-treated Addison's disease, it appeared that the activity of the thyroid was slightly below normal (34).

In the present series the I^{131} accumulation gradient in 28 patients with

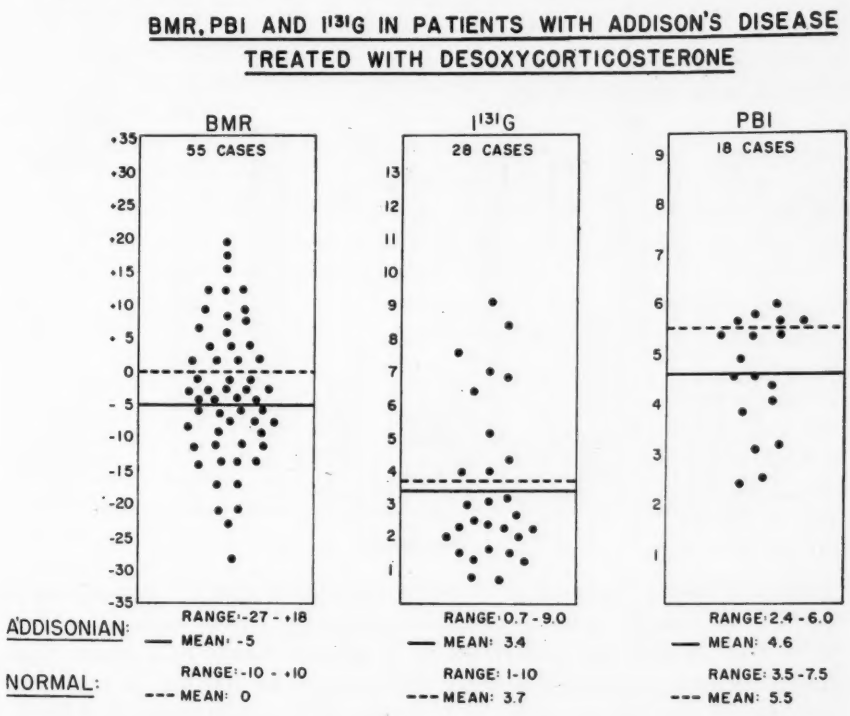

FIGURE 7

Addison's disease ranged from 0.7 to 9.0 with a mean of 3.4. Serum protein-bound iodine levels in 18 patients with Addison's disease ranged from 2.4 to 6.0 gamma per cent. Basal metabolic rates in 55 patients with Addison's disease ranged from minus 27 per cent to plus 18 per cent, with a mean value of minus 5 per cent. The range was between minus 10 per cent and

plus 10 per cent in 64 per cent of these patients, greater than plus 10 per cent in 11 per cent of patients, and less than minus 10 per cent in 25 per cent of the patients (Fig. 7).

ACTH administered to 2 patients with Addison's disease for forty-eight hours induced no adrenal cortical response in that period, as measured by the change in circulating eosinophils and urinary 17-ketosteroid excretion (23), and no thyroid response was obtained as measured by the change in I^{131} gradient, serum protein-bound iodine and basal metabolic rate.

Cortisone acetate, 50–100 mg. per day, administered to 8 patients with

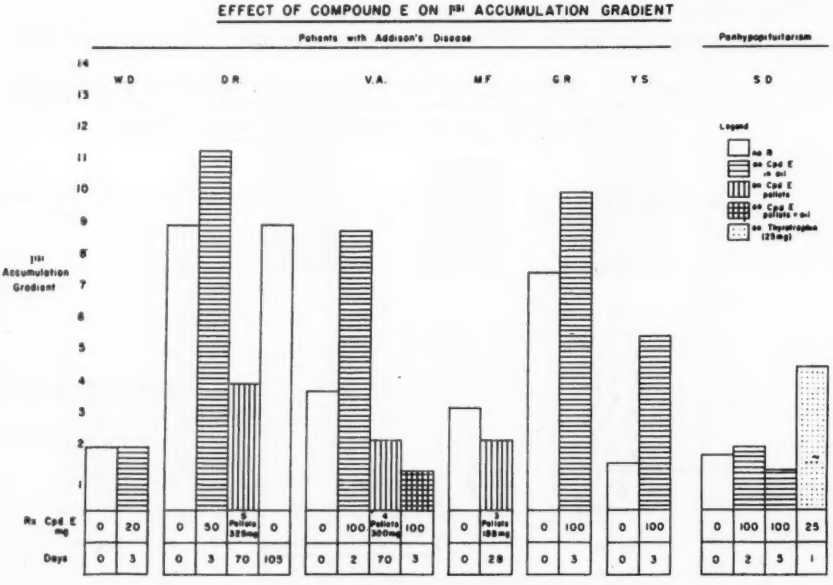

FIGURE 8

Addison's disease, induced a transient increase in the I^{131} accumulation gradient of from 30 to 100 per cent for a period of two or three days (Fig. 8) in 4 of the patients, a decrease in 2, and no change in 2 others. The initial increase in thyroid activity following 50 to 100 mg. of cortisone acetate per day did not occur in 1 patient with anterior pituitary insufficiency, although a response to *TSH* was obtained (Fig. 8). The initial rise in the I^{131} gradient was followed by a more persistent decrease, usually below the initial value. Serum protein-bound iodine levels tended to decrease slightly, whereas basal metabolic rates remained unchanged or increased slightly. Cortisone acetate administered to 1 patient in doses of only 20 mg. per day induced no change in I^{131} accumulation gradient. One

adolescent girl with severe Addison's disease, given cortisone acetate in doses of 10 mg. per day for one month, followed by implantation of 548 mg. of cortisone acetate pellets, had a progressive increase in I^{131} accumulation gradient of from 2.5 to 39.4, in basal metabolic rate from minus 7 per cent to plus 13 per cent, and in serum protein-bound iodine from 3.6 to 18.3 gamma per cent with a marked increase in the size of the thyroid gland.

The implantation of cortisone acetate *pellets* (ranging in aggregate weight from 400 to 1,000 mg.) in 10 patients with Addison's disease induced no change in I^{131} accumulation gradient in 2 patients; in 3 patients, including the one mentioned above, there was a marked increase in I^{131} gradient over a two-month period, whereas in another there was a decrease in I^{131} gradient in thirty days, with a subsequent increase in fifty days. In 4 other patients there was a decrease in the I^{131} gradient. Serum protein-bound iodine levels which were followed in 6 patients did not change significantly one month following pellet implantation. Basal metabolic rates tended to increase slightly.

Summary: These results suggest that in the majority of patients with Addison's disease the I^{131} accumulation gradient, serum protein-bound iodine level and basal metabolic rate fall within normal limits, but that the mean values for the group are slightly below the corresponding mean values for a group of normal subjects.

It would appear that forty-eight hours of ACTH administration elicits no adrenal cortical or thyroid response in patients with Addison's disease, whereas cortisone acetate in doses of 50–100 mg. per day may induce an initial increase in I^{131} gradient in some instances. This increase (not obtained in 1 patient with panhypopituitarism) was usually followed by a levelling off or a decrease in the I^{131} gradient. Serum protein-bound iodine levels tended to decrease slightly, whereas basal metabolic rates remained unchanged or increased slightly. Doses of 10 to 20 mg. per day elicited a variable thyroid response in Addisonian patients. Cortisone acetate pellets in dosage not exceeding 10 mg. of cortisone acetate liberated per day, induced no consistent change in I^{131} accumulation gradient or serum protein-bound iodine and led to a slight increase in basal metabolic rate.

Cushing's syndrome

In 5 patients with classic active Cushing's syndrome, thyroid function was normal as measured by I^{131} accumulation gradient and basal metabolic rate. In 3 of these patients serum protein-bound iodine levels were measured and found to be normal (Table 1).

In 3 of the patients serial determinations of I^{131} uptake were made over a prolonged period of time and, although usually constant, they were noted

to be decreased by 60 to 84 per cent in all 3 patients at the time of a clinical exacerbation of their disease.

TABLE 1. THYROID FUNCTION IN CUSHING'S SYNDROME

Patient	Sex	Age (yrs.)	PBI (gamma %)	BMR %	I^{131} G
E.B.	F	39	4.8	−10	2.0
M.C.	F	39		−6	3.1
E.H.	F	39	4.7	+5	2.7
L.D.	F	37		+2	4.0
G.W.	M	28	3.9	−6	3.1

ACTH administered for twenty-four and again for thirty-six hours to a 29-year-old female patient with untreated Cushing's syndrome (E.B.) induced a marked adrenal cortical response as measured by a sevenfold increase in urinary 17-ketosteroid and formaldehydogenic steroid excretion. Concurrently, there was a decrease in I^{131} accumulation gradient from 1.9 to 0.5, no change in serum protein-bound iodine and an increase in basal metabolic rate from minus 16 per cent to minus 7 per cent (Fig. 9).

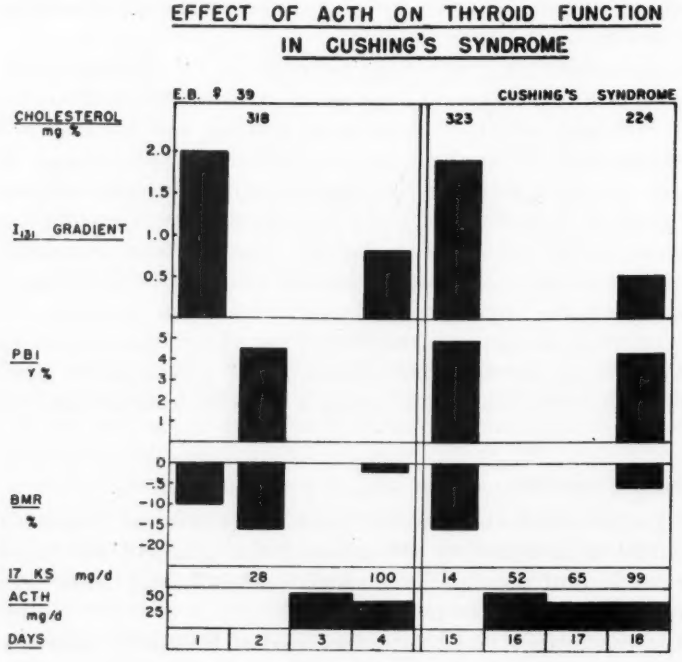

FIGURE 9

Summary: Although thyroid function appears to be normal in patients with Cushing's syndrome, such patients may have a decrease in I^{131} accumulation gradient with a constant serum protein-bound iodine level and an increase in basal metabolic rate during a clinical relapse or following ACTH administration.

THE RESPONSE OF THE ADRENAL CORTEX TO THE FOUR HOUR ACTH TEST IN PATIENTS WITH HYPOTHYROIDISM AT VARYING LEVELS OF BASAL METABOLIC RATE

			BEFORE TREATMENT			AFTER THYROID HORMONE TREATMENT		
PT.	SEX	AGE	BMR	EOS % change	U.A/CREAT. % change	BMR	EOS % change	UA/CREAT. % change
NORMAL			0	-85	+90			
P.W.	M	46	-24	+11				
M.R.	M	49	-30	+4	-13	+6	-43	+36
M.S.	M	58	-38	-36	+35			
F.McC.	F	63	-19	-93				
M.W.	F	64	-20	-34	+15			
V.McD.	F	49	-21	-54	+69	+20	-66	+120
F.L.B.	F	47	-30	-24				
M.O'C.	F	58	-31	-41				
C.P.	F	52	-36	-24	+26	-14	-77	+69
F.B.	F	37	-36	-21				

FIGURE 10

Hypothyroidism

Relation of adrenal cortical response to thyroid activity: Nine of 11 patients with hypothyroidism given a single 25 mg. injection of *ACTH* had an inadequate adrenal cortical response (23), as measured by the four-hour decrease in circulating eosinophils and increase in uric acid-creatinine ratio. Three of these patients were given a similar test following *thyroid hormone* (desiccated thyroid) therapy, at which time their response had reverted either to or toward normal (Fig. 10), whereas the adrenal response of 2 others similarly tested was unchanged following thyroid hormone therapy.

Eight out of 10 patients with hypothyroidism had an initially low urinary 17-ketosteroid excretion. Seven out of these 10 had an inadequate or delayed response to forty-eight hours of ACTH administration as

measured by the increase in urinary 17-ketosteroid excretion (Fig. 11). When the more sensitive circulating-eosinophil decrease was used as a criterion of adrenal cortical response, only 3 had an inadequate response in forty-eight hours. One patient with untreated hypothyroidism, who showed a delayed rise in urinary 17-ketosteroid excretion during forty-eight

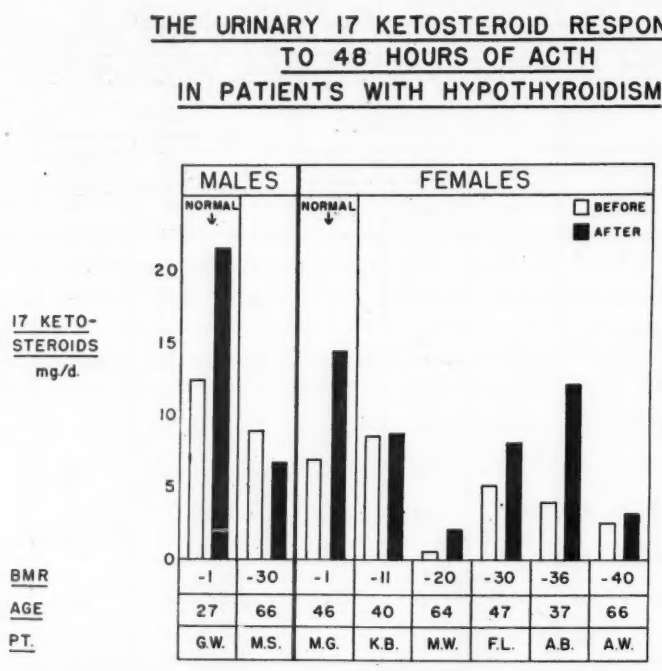

FIGURE 11

hours of ACTH, responded more promptly following administration of desiccated thyroid and a consequent rise in basal metabolic rate (Fig. 12). Another patient with myxedema whose 17-ketosteroids did not respond to forty-eight hours of ACTH administration prior to thyroid hormone therapy did have a response as measured by an increase in both 17-ketosteroids and basal metabolic rate following therapy (Fig. 13). Two other patients with myxedema who failed to respond to forty-eight hours of ACTH administration prior to thyroid hormone therapy also failed to respond to similar adrenocortical stimulation following adequate thyroid hormone replacement therapy.

The effect of adrenal cortical steroids on oxygen consumption: In order to gain insight into the effect of the adrenal cortical hormones on the periph-

THE 17-KETOSTEROID RESPONSE TO 48 HOURS OF ACTH IN A PATIENT WITH HYPOTHYROIDISM BEFORE AND AFTER TREATMENT WITH THYROID

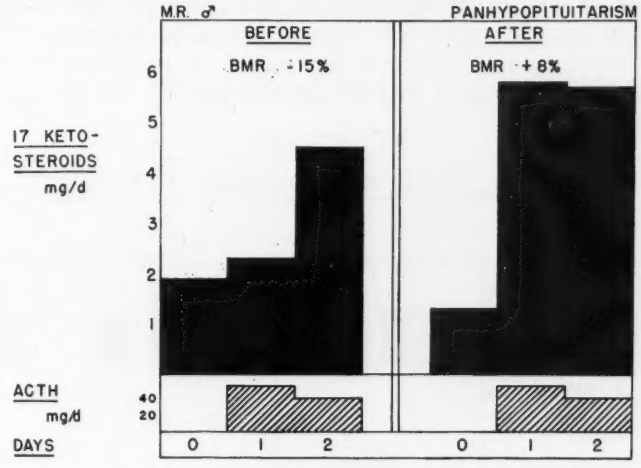

FIGURE 12

THYROID AND ADRENAL RESPONSE TO ACTH

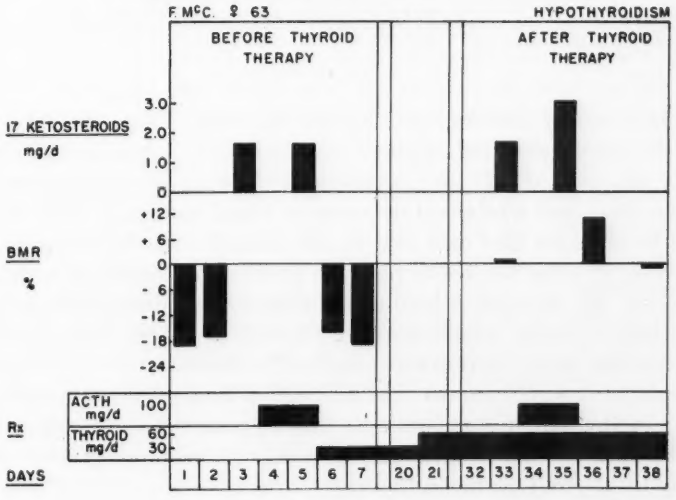

FIGURE 13

eral action of thyroid hormone, 2 athyreotic individuals who took thyroid medication regularly were chosen for study. A 19-year-old male with congenital athyreosis, taking 180 mg. of desiccated thyroid a day, was given 80 mg. of *ACTH* (20 mg. every six hours) for five days and 160 mg of ACTH (40 mg. every six hours) for two days intramuscularly (Fig. 14). A female (F.L.), aged 47, with postoperative hypothyroidism, receiving a suboptimal dose of 30 mg. of thyroid hormone per day, was given *cortisone*

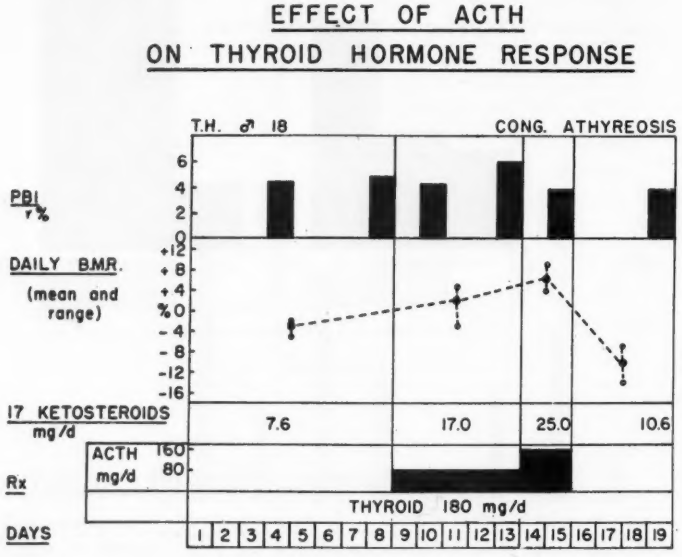

FIGURE 14

acetate in doses of 200 mg. per day for five days (Fig. 15). Daily basal metabolic rates increased slightly, but definitely, during the period of activity of both ACTH and cortisone. Following discontinuance of the hormone there was a rebound decrease in basal metabolic rate below the control level in the first case and to the control value in the second case. The change in basal metabolic rate was greater than could be explained on the basis of the decrease in nonprotein respiratory quotient accompanying ACTH and cortisone administration. In both instances there was no consistent change in serum protein-bound iodine level.

Summary: It would appear that adrenal cortical response is delayed and at times inadequate in some patients with hypothyroidism. A more prompt and adequate adrenal cortical response may be restored in some of these patients by thyroid hormone therapy.

These studies suggest that both ACTH and cortisone acetate are capable

of increasing the basal metabolic rate without changing the serum protein-bound iodine level in patients taking a constant dose of thyroid, in the absence of any endogenous compensating mechanism.

THE EFFECT OF CORTISONE ON THYROID FUNCTION IN A PATIENT WITH MYXEDEMA RECEIVING SUBOPTIMAL DOSES OF THYROID HORMONE

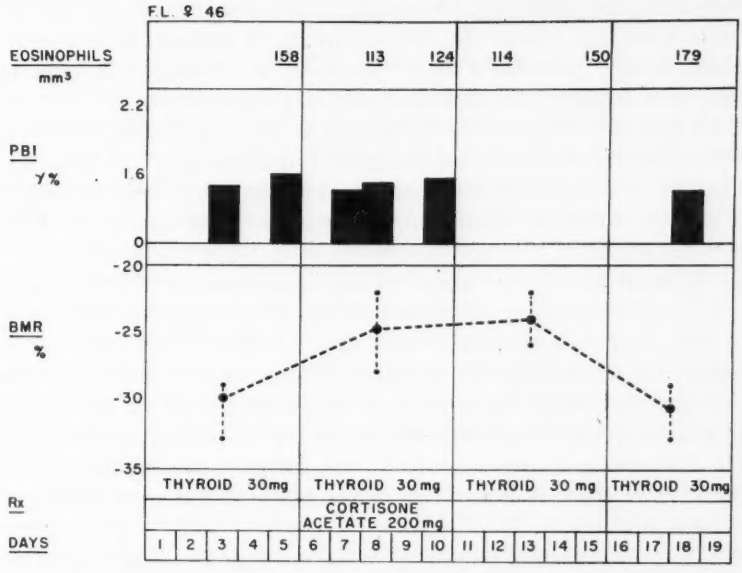

FIG. 15. The basal metabolic rates in each period represent the mean and range of daily determinations. The milligrams of thyroid and cortisone refer to the daily dose administered.

Hyperthyroidism

Six patients with classic Graves' disease given a single injection of 25 mg. of *ACTH* showed a normal adrenal cortical response, as measured by the 4-hour fall in circulating eosinophils. Three out of 5 of these patients had an adequate adrenal cortical response to ACTH administration, as measured by the 48-hour increase in urinary 17-ketosteroid excretion. The 2 patients who failed to respond adequately in forty-eight hours, subsequently had an adequate increase in urinary 17-ketosteroids following more prolonged ACTH administration.

Six patients with Graves' disease were treated with ACTH in doses of 40 to 200 mg. per day for five to twenty-three days. The degree of adrenal

cortical response, as measured by the increase in urinary 17-ketosteroid excretion, was variable; the maximum excretion ranged from 17.7 to 65.9 mg. per twenty-four hours following five to twelve days of ACTH administration.

Five of these 6 patients treated with ACTH had a decrease in "iodine space," and 3 of the 6 had a decrease in I^{131} accumulation gradient. Three of 5 patients had a decrease in serum protein-bound iodine, whereas only 2 of the 6 had a significant decrease in basal metabolic rate. Three patients of the 6 had a decrease in gland size and improvement in clinical symptoms. Creatine tolerance tended to increase in the 2 patients in whom it was followed. Serum cholesterol levels, which were followed in 2 patients, remained unchanged in one and decreased slightly in another.

In all patients there was an initial period of increased thyrotoxicity for four to twenty-four hours following the initiation of ACTH therapy. In 5 cases the I^{131} accumulation gradient and serum protein-bound iodine were measured during this period of increased thyrotoxicity and found to be slightly elevated in 2 and decreased in 3. Basal metabolic rates were elevated in all during this period of increased toxicity. The following details in the clinical course of these patients deserve special mention.

In A.F., a 52-year-old female with Graves' disease of at least one year's duration, the administration of 80 to 120 mg. of ACTH per day for ten days failed to change the clinical or laboratory signs of thyrotoxicosis. Only a moderate adrenal cortical response was obtained, as indicated by a rise in 17-ketosteroid excretion to 21 mg. per day. The results of a biopsy of the thyroid gland obtained before and after ACTH were interpreted as showing no change.

In C.J., a 35-year-old female with Graves' disease of one year's duration, 40 to 200 mg. of ACTH per day for twenty-five days failed to change the state of thyroid function, although an adequate adrenal cortical response was obtained as evidenced by a rise in 17-ketosteroid excretion to 46.8 mg. per day. There was a slight increase in creatine tolerance.

I.M., a 29-year-old male with classic hyperophthalmopathic Graves' disease of one and a half years' duration, was treated for fourteen days with 40 to 200 mg. of ACTH per day. A delayed, but adequate, adrenal cortical response was obtained, as measured by a rise in 17-ketosteroids to 45 mg. per day. ACTH induced a moderate decrease in serum protein-bound iodine, in congestive eye symptoms and in the size of the thyroid gland, without other evidence of improvement in the thyrotoxicosis.

In H.H., a 45-year-old female with mild thyrotoxicosis of six years' duration, the administration of 40 mg. of ACTH per day for five days induced a moderate adrenal cortical response as measured by a rise in 17-ketosteroids to 17.7 mg. per day. A decrease in I^{131} accumulation gradient, thyroid

gland size and an improvement in the clinical picture was also induced. Following discontinuance of ACTH, a clinical exacerbation occurred which proved to be transitory. Thereafter, there was a spontaneous remission in the disease, so that three months later this patient had a normal I^{131} accumulation gradient and clinically appeared normal.

H.A., a 20-year-old female with Graves' disease of one year's duration was treated with 80 to 120 mg. of ACTH per day for seventeen days,with only moderate adrenal cortical response, as measured by a rise in 17-ketosteroids to 17.7 mg. per day. ACTH induced a decrease in I^{131} accumulation gradient, serum protein-bound iodine and size of the thyroid gland. Results of a biopsy of the thyroid gland obtained before and after ACTH were interpreted as showing marked involution following therapy.

In C.O., a 33-year-old female with thyrotoxicosis of only two months' duration, 50 to 80 mg. of ACTH per day for fourteen days induced a marked adrenal cortical response, as evidenced by a rise in 17-ketosteroid excretion to 65.9 mg. per day and an almost complete remission in her thyrotoxicosis, as evidenced by both clinical and laboratory findings. This patient underwent a subtotal thyroidectomy, with fourteen days of ACTH administration as the only preoperative preparation. Prior to ACTH, the estimated weight of the thyroid gland was 75 to 80 grams. At operation four-fifths of the thyroid was removed and the specimen weighed 8 grams. The histologic appearance was interpreted as showing partial thyroid involution and there was no lymphocytic infiltration of the gland (Fig. 16).

One patient, C.J., was treated with *cortisone acetate* in doses of 100 to 200 mg. per day for sixteen days. There was no change in I^{131} accumulation gradient or clinical picture, although there was a decrease in serum protein-bound iodine and basal metabolic rate. There was a slight decrease in serum cholesterol; creatine tolerance was markedly decreased (Fig. 17). ACTH was subsequently given to this patient, as noted above, without producing any effect on thyroid function.

Summary: The adrenal cortical response to ACTH in the hyperthyroid state appears to be normal in most instances. Following an initial exacerbation of clinical hyperthyroidism (manifested chiefly by an increase in basal metabolic rate) both ACTH and cortisone appear to suppress thyroid function in about one half of the patients with Graves' disease in this limited series. The best results correlate with the shortest duration of the hyperthyroid state and greatest degree of adrenal cortical response.

Exophthalmos

Four patients with marked exophthalmos were treated with 40 to 80 mg. of *ACTH* per day for fourteen to nineteen days.

Two patients were euthyroid at the time of study. In both, the exophthalmos developed following subtotal thyroidectomy for thyrotoxicosis. Both had subjective relief of pain and a sense of decreased eye pressure following ACTH administration. There was objective relief of chemosis, excess lacrimation and conjunctival injection, together with an increased ability to close the lids. Exophthalmometric measurements with the Luedde

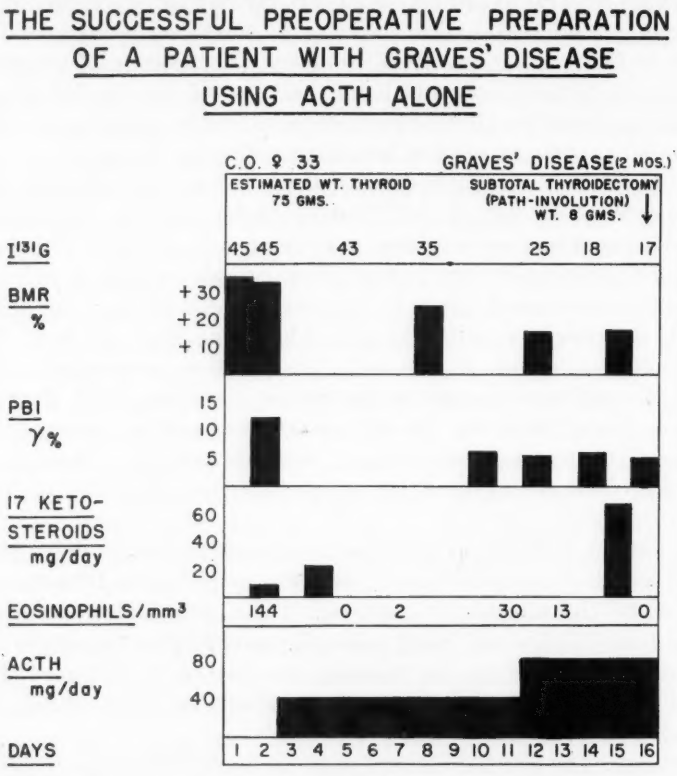

FIGURE 16

exophthalmometer were unsatisfactory, although there was an apparent decrease in exophthalmos in both patients of from 2 to 4 mm. Ocular myopathies persisted. In one patient there was an exacerbation of exophthalmos following discontinuance of ACTH. In the other patient, improvement was maintained following x-irradiation of the orbits, together with estrogen therapy.

Another patient with marked exophthalmos was euthyroid with no history of thyrotoxicosis. Definite subjective, but only slight objective improvement took place in the exophthalmos. There was, however, a considerable decrease in conjunctival edema and injection.

One patient, I.M., with exophthalmos and thyrotoxicosis, had moderate subjective and objective relief of pain, redness and lacrimation during ACTH administration. The only improvement observed in thyrotoxicity, however, was a slight decrease in serum protein-bound iodine and size of the thyroid gland.

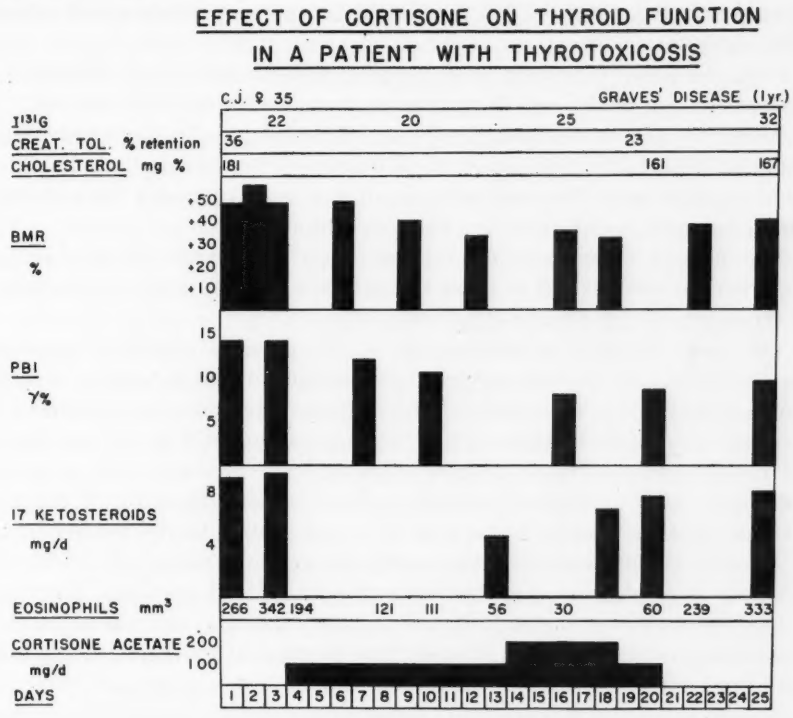

FIGURE 17

Summary: The administration of ACTH appears to induce a slight to moderate improvement in hyperophthalmopathic Graves' disease. This improvement occurs in both the so-called thyrotropic and thyrotoxic varieties of exophthalmos (35) and consists chiefly of a reduction in the congestive symptoms with little or no measurable effect on the exophthalmos.

DISCUSSION

From the present studies and the experience of many other investigators (1–29), evidence has been obtained which strongly suggests a close interrelationship between the thyroid and adrenal glands.

We consider the I^{131} accumulation gradient a measure of iodine uptake and turnover within the thyroid gland, the serum protein-bound iodine

as an indication of the quantity of circulating thyroid hormone, and the basal metabolic rate a measure of the tissue response to thyroid hormone or other calorigenic agents. By the use of these tests, a three-dimensional picture of thyroid function is obtained. In the present studies, changes in serum cholesterol levels possess limited value in interpreting changes in thyroid activity, since ACTH is thought to exert an independent action upon cholesterol (36).

From the present study it would appear that an increase in circulating adrenal steroids elicits two distinct alterations in thyroid function, *viz.*, 1) a calorigenic action, associated with an increased basal oxygen consumption, and 2) an inhibitory action on all phases of thyroid function. To date, some patients with the nephrotic syndrome and Addison's disease constitute the only major exception to these findings.

The increase in oxygen consumption following adrenal steroid therapy is evident to some extent in all of the patients studied, with the exception of those with the nephrotic syndrome (37).

The most obvious substantiation of the possible ability of adrenal cortical steroids to increase oxygen consumption without increasing thyroid hormone utilization was obtained in 2 athyreotic patients maintained on a constant dose of desiccated thyroid while receiving ACTH and cortisone. All patients demonstrated a small but significant increase in basal metabolic rate, with a rebound decrease following discontinuance of adrenal steroids, with no change in the level of serum protein-bound iodine. In all of these determinations the basal metabolic rate was corrected for the alterations in respiratory quotient induced by ACTH or cortisone therapy.

In subjects with a normal thyroid-pituitary axis the increase in oxygen consumption due to adrenal steroids may be masked by their concomitant inhibitory effects on thyroid function. It can, however, be appreciated even in normal subjects if it is realized that at a time when both the I^{131} accumulation gradient and serum protein-bound iodine are slightly to moderately decreased, the basal metabolic rate either remains unchanged or increases. During more prolonged adrenal steroid therapy, when the decrease in serum protein-bound iodine and I^{131} accumulation gradient becomes more marked, the basal metabolic rate also decreases, but not to the extent that one would anticipate.

The calorigenic effect of adrenal steroids may be the result of an increased peripheral effectiveness of thyroid hormone and/or a direct calorigenic effect of the adrenal steroids. It is apparently not the result of increased utilization of thyroid hormone.

The second phase of adrenal steroid influence on thyroid function is an inhibitory one in which all aspects of thyroid function are depressed. This inhibitory effect was demonstrated to some extent by all of the subjects studied, especially the normal subjects and patients with Cushing's

syndrome. It was also demonstrated by an occasional patient with classic thyrotoxicosis, who was given ACTH or cortisone. Such inhibitory changes could best be explained by assuming that a constant high level of adrenal steroids induced pituitary inhibition of both ACTH (38) and TSH production. Such a theory would imply that patients in whom the thyrotoxicosis was dependent upon increased TSH production would be the most susceptible to this mechanism, and that patients with thyrotoxicosis arising primarily within the thyroid gland would prove refractory.

That the thyroid-inhibitory effect of adrenal steroids occurs as a result of pituitary inhibition and not through peripheral or end-organ inhibition of TSH is suggested by the fact that administered TSH is capable of stimulating a thyroid response following inhibition of the thyroid by, and in the presence of, a high level of adrenal steroids. The data presented do not preclude the possibility that adrenal steroids might have some other inhibitory effect on thyroid tissue independent of TSH.

The suppression of thyroid activity by ACTH leads to a gradual reduction in BMR during prolonged high dosage therapy with this agent. Since adrenal cortical activation is definitely reduced with a lowering of the BMR and since general metabolic activity is decreased, one might expect to find a gradual unresponsiveness to ACTH during prolonged courses of therapy. Thus, the effect of decreased thyroid function must always be thought of as a possible cause for a gradually developing unresponsiveness to ACTH.

The accumulation gradient was chosen as a criterion since it did reveal definite changes under ACTH or cortisone therapy. Whenever 24-hour iodine uptakes were also determined it was found that they did not change, confirming previous observations by Knowlton, *et al.* (39). It would appear that with the suppression of TSH secretion, iodine uptake is merely retarded rather than inhibited completely.

The changes in thyroid activity induced by the administration of cortisone to patients with Addison's disease are comparable to those seen in normal subjects. There is, however, in some cases a transient increase in I^{131} accumulation gradient, basal metabolic rate, and a decrease in serum protein-bound iodine, suggesting an increased utilization of, and demand for thyroid hormone. This increase in thyroid function is usually temporary, but occasionally is progressive despite continued cortisone therapy. Indeed, in 1 adolescent girl, thyrotoxicosis was apparently initiated by this mechanism.

This increase in thyroid function has not been observed in all patients with Addison's disease and does not occur if they have had adrenal extract therapy immediately prior to cortisone administration. In these situations the thyroid response is comparable in every respect to that seen in normal subjects following adrenal steroid therapy.

SUMMARY AND CONCLUSIONS

1. An attempt has been made to evaluate the effect of ACTH and of cortisone on thyroid function, as well as to follow thyroid and adrenal activity in various disease states.

2. In the present studies the I^{131} accumulation gradient has been used to indicate the iodine uptake and turnover within the thyroid gland, the serum protein-bound iodine to indicate the quantity of circulating thyroid hormone, and the basal metabolic rate to measure the tissue response to thyroid hormone or other calorigenic agents.

3. In normal subjects, ACTH and cortisone appear to induce a depression of the I^{131} accumulation gradient and serum protein-bound iodine. The basal metabolic rate either increases, remains unchanged or decreases, depending upon the degree of thyroid depression. In contrast, ACTH and cortisone may induce an increase in I^{131} gradient and serum protein-bound iodine, if the latter value is initially low, while inducing a slight decrease in the basal metabolic rate in patients with the nephrotic syndrome.

4. Exogenous thyroid-stimulating hormone (TSH) is capable of eliciting a thyroid response following inhibition by and in the presence of a high level of adrenal cortical steroids.

5. The majority of patients with Addison's disease have normal I^{131} accumulation gradients, serum protein-bound iodine levels and basal metabolic rates. The mean values of these determinations are, however, slightly below the corresponding mean values for a group of normal subjects.

6. In some patients with Addison's disease, cortisone acetate may induce an initial increase in thyroid activity which may be followed by a more persistent decrease if cortisone is continued.

7. Patients with Cushing's syndrome have normal thyroid function, which, however, is markedly depressed upon a further increase in adrenal cortical steroids, either spontaneous or induced by ACTH.

8. Some patients with hypothyroidism exhibit a delayed, and at times inadequate adrenal cortical response to ACTH, which may be restored to normal by thyroid hormone therapy in some instances.

9. ACTH or cortisone induce a slight but definite increase in the basal metabolic rate (by a calorigenic action) without changing the thyroid hormone level, in athyreotic patients receiving a constant dose of desiccated thyroid.

10. The majority of patients with hyperthyroidism have a normal adrenocortical response to ACTH administration.

11. Following an initial exacerbation of hyperthyroidism, both ACTH and cortisone appear to depress thyroid function in some patients with Graves' disease. The best results correlate with the shortest duration of the hyperthyroid state and greatest degree of adrenal cortical response.

12. ACTH appears to induce a slight, temporary, clinical improvement

in both the so-called thyreotropic and thyrotoxic varieties of exophthalmos.

13. Adrenal steroids appear (a) to have a calorigenic action and (b) to suppress thyroid activity through pituitary inhibition. Their effect on the basal metabolic rate appears to be a resultant of these two opposing actions.

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FUNCTION OF THE ADRENAL CORTEX IN MYXEDEMA, WITH SOME OBSERVATIONS ON PITUITARY FUNCTION*

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AS OUR knowledge of thyroid and pituitary function developed, it became clear that there are two types of myxedema—one due to primary thyroid failure and the other due to pituitary failure with secondary thyroid atrophy. A differential diagnosis between these two conditions is always difficult and can be made only after careful evaluation of clinical and laboratory data. In the diagnosis of pituitary myxedema considerable weight is given to the concomitant absence or diminution of the various tropic hormones of the pituitary, or of adrenocortical failure. However, interpretation of data is made difficult by the knowledge that primary myxedema may of itself depress pituitary and adrenal function. Consequently, this study was initiated to determine to what degree the pituitary and adrenals are affected by primary myxedema.

In the literature there is a limited amount of data on this subject. Friedgood (1) demonstrated low excretion of 17-ketosteroids in the urine of 10 patients with spontaneous and post-thyroidectomy myxedema. Therapy did not raise the values. Talbot *et al.* (2) demonstrated low normal 17-ketosteroid values in 9 hypothyroid children, and subnormal values in 3. Engstrom and Mason (3) reported diminished excretion in 13 cases. In the 10 cases of spontaneous myxedema there was no change following therapy up to one year, but in the 3 post-thyroidectomy cases there was an increase. One patient with myxedema had an elevated excretion. Escamilla (4), on the other hand, reported a somewhat higher than normal level in 4 women with hypothyroidism and a low level in 1 myxedematous male.

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TABLE 1. RESULTS OF SOME OF THE TESTS MEASURING ADRENAL AND PITUITARY FUNCTION BEFORE AND AFTER THYROID THERAPY

Case No.	Age (yrs.)	BMR %	PBI γ%	Cholesterol, mg. %	17-KS, mg./24 hrs.	11-OCS, mg./24 hrs.	Na mEq./L	Cl mEq./L	K mEq./L	FSH mouse units	Treatment interval (years)	17-KS, mg./24 hrs.	11-OCS, mg./24 hrs.	Na mEq./L	Cl mEq./L	K mEq./L	FSH mouse units
										Males							
1	40	−40		619	5.2		138	105	4.9	Pos. 6.5 Neg. 13, 96	7/12	4.5		142	98	4.4	Pos. 6.5, 13 Neg. 52
4	36	−37		259	4.0	0.06	126	94	4.2	Neg. 6.5, 13, 52	3/12	4.5	0.029	140	102	5.1	Pos. 3, 6.5 Neg. 13, 26
10	53	−45		321	8.7					Neg. 100	10	7.0					Pos. 6.5, 13
16	49	−38	1.3	200	2.5					Pos. 6.5	7	3.4					
26	74	−56		260	4.2		136			Pos. 13, 26 Neg. 52							
36	53	−25		364	4.4		139	102		Pos. 6.5							
										Premenopausal Females							
2	47	−39		280	1.4	0.21	135	94	4.4		7/12	2.6	0.09	141	100	6.3	
6	17	−45		501	2.7		138	102	4.5	Neg. 6.5, 13	3/12	4.6		135	106		Pos. 6.5, Neg. 13
8	41	−39		242	2.0					Pos. 6.5, 13 Neg. 104	6	5.6					Neg. 13, 52
9	42	−44		466	2.2		144			Neg. 100	7	3.8					Pos. 13
15	29	−50		292	3.8		140	100		Neg. 6.5, 13, 26	7	8.2					Pos. 3 Neg. 6.5
30	41	−46		500	1.0	0.13	138	92		Neg. 6.5, 13, 104	2/12						
33	36	−45		396	2.9												
34	40	−46	0.7	291	2.9					Pos. 3, 6.5 Neg. 96, 192							
39	30	−41									3/12	7.5					
										Menopausal Females							
3	71	−28		493	2.3		138	98		Pos. 6.5, 13, 52, 104							
5	59	−40	0.3	207	0.8		139	105	5.0	Pos. 13, 48, 96 Neg. 192	2[2]/12	1.4		141	102	4.8	Pos. 96, 192
7	45	−48		410	3.6		140	95		Pos. 6.5, 52	7	2.2					Pos. 26 Neg. 52, 104
11	47	−48	0.8	384	1.3												
12	49	−56		568	1.4					Neg. 100	8	1.7					Pos. 6.5, 13 Neg. 52, 104
13	45	−23			2.5					Pos. 6.5, 13, 26, 52 Neg. 104							
14	69	−40		405	1.3	0.09	137	99		Pos. 13, 48, 96 Neg. 192	4	2.1	0.431	142	99		Pos. 96, 192
										Pos. 6.5, 13 Neg. 104							Pos. 96, 192, 384 Neg. 576
17	56	−44		442	1.2					Pos. 78 Neg. 236	10/12	3.1					
18	63	−34		260	0.3		143			Neg. 100	8	1.3					Pos. 13, 52, Neg. 104
19	61	−35		245	2.6		149	94			10/12						Neg. 6.5, 13
											6	1.2					Pos. 6.5, 52, 104
20	56	−34		342	1.6					Pos. 96, 192	3	1.0					
21	52	−36		186	2.6						7	3.2					
22	50	−37		471	2.7		137			Pos. 100	8	2.9					
23	64	−37		387	2.1		140			Neg. 100							
24	53	−36	2.0	532						Pos. 6.5, 13	2						Pos. 6.5, 13, 52, 104
25	55	−35	0.7	175	0.8												
27	50	−49	1.8	208	1.2		138	97		Pos. 6.5, 13 Neg. 104	5	2.9					Pos. 6.5, 13, 52, Neg. 104
28	58	−29		320	7.5	0.2											
29	60	−43	0.6	316	0.9		141	90	5.6	Pos. 6.5							
31	51	−37		316						Pos. 6, 13, 26, 52	2	3.7					Pos. 6, 13, 26, 52, ±104
											7	6.6					
32	49	−37		316						Pos. 100							
35	50	−45		300	1.3		142			Pos. 13, 26, Neg. 52	1/12			144			
37	55	−40		300	4.9												
38	76	−41		335						Pos. 6, 13							
40	77	−40		624	2.9												
41	60	−43		392	2.1					Pos. 6.5, 13, 26 Neg. 52							
42	65	−35		254	6.1												
43	41	−49	1.5	197	0.7		138	103	3.7	Pos. 3, 6.5 Neg. 13, 26	6/12						Neg. 13, 26, 52
											3[1]/12	0.6		139	96	5.7	Pos. 6.5, 13 Neg. 52, 104
																	Pos. 6.5, 13, ±52 Neg. 104

Excretion of 11-oxycorticosteroid-like substances was found to be low by Talbot *et al.* (5) in 2 women. In 1, the level of excretion returned to normal after thyroid therapy.

Stephens (6) found the salt depletion test (Cutler-Power-Wilder) to give normal results in 6 patients with myxedema, in 2 of whom the condition was post-thyroidectomy. Levy *et al.* (7) reported on the water diuresis test (Kepler) in 3 patients with myxedema. In only 1 was there a positive response to the second portion of the test.

METHOD OF STUDY

In this study, we have attempted to exclude all cases of pituitary myxedema or panhypopituitarism, on the basis of laboratory tests and careful clinical observations by many observers over long periods of time. Only those patients were included in whom the full-blown clinical picture of myxedema was present. Various tests measuring the function of the thyroid and adrenals, and a few tests measuring the function of the pituitary were performed while the patients were myxedematous. These tests were repeated when the patients were euthyroid for varying periods of time. The thyroid function was measured by basal metabolic rate, blood cholesterol, serum protein-bound iodine, and by roentgenograms of the epiphyses when indicated. The pituitary status was determined by excretion of follicle-stimulating hormone in the urine, insulin-tolerance test, eosinophil response to adrenalin, and menstrual history. The various hormones of the adrenal cortex were tested by 17-ketosteroid excretion, 11-oxycorticosteroid excretion, eosinophil response to adrenalin, insulin-tolerance test, determination of blood electrolytes and the Cutler-Power-Wilder test.[1] The insulin-tolerance tests were performed as described by Fraser *et al.* (8) after preliminary preparation with three days of high carbohydrate (350 Gm.) diet. Eosinophil counts were made on capillary blood and the diluent was 0.1 per cent phloxine in propylene glycol. Counts were made in four chambers of the special Levy chamber for each determination.

RESULTS

In Table 1 are listed the results of all laboratory studies before and after therapy, with the exception of the insulin-tolerance test, Cutler-Power-Wilder test, and the eosinophil response to adrenalin. The patients have been grouped according to sex and the females have further been divided into the premenopausal and menopausal groups. The dose of thyroid administered varied but was ordinarily sufficient to make the patient clinically euthyroid. Basal metabolic rates after therapy, although

[1] We are indebted to Dr. Douglas Riggs for the blood iodine determinations, to Dr. Fuller Albright for the FSH and 17-ketosteroid determinations and to Dr. N. B. Talbot for the 11-oxycorticosteroid determinations.

not shown in the chart, were mostly between minus 15 per cent and 0. In many cases, the dose of thyroid was purposely not given to the limit of tolerance because of the age of the patient or because of the necessity for avoiding the ill effects of coincident coronary artery disease.

Duration of the disease. It was difficult in most cases to be sure of the duration of the disease since the onset was usually insidious. There was no correlation between the duration of symptoms, and the values of the

TABLE 2. CHANGE IN EXCRETION OF 17-KETOSTEROIDS AFTER THYROID THERAPY IN FEMALES

Case No.	Increase, mg./24 hrs.	Decrease, mg./24 hrs.
	Premenopausal	
2	1.2	
6	1.9	
8	3.6	
9	1.6	
15	4.4	
	Menopausal	
5	0.6	
12	0.3	
14	0.7	
17	1.9	
18	1.0	
21	0.6	
22	0.2	
27	1.7	
31	2.9	
7		1.4
19		1.4
20		0.6

various tests, with possibly three exceptions. Patient #39 had a thyroidectomy five months prior to the diagnosis of myxedema. In patient #42 symptoms of myxedema developed rather abruptly, following cholecystectomy one and one-half months previously. The 17-ketosteroid excretions in these cases were 7.5 mg. and 6.1 mg. respectively. Patient #10, mentioned later, had a 17-ketosteroid value of 8.7 mg. per twenty-four hours.

17-Ketosteroids. The levels of 17-ketosteroid excretion in the males were definitely low, the average excretion for the 6 males being 4.8 mg. There was no significant change in excretion level following therapy. Patient #10, in whom the level was within normal range, was clinically described as an "early case." However, the basal metabolic rate and blood cholesterol were well within the range seen in myxedema.

The average excretion in the 9 premenopausal females was 2.4 ± 0.30 mg. in twenty-four hours. The value in each case was considerably below the normal range for females, but not as low as those commonly seen in panhypopituitarism. As shown in Table 2, there was an increase in excretion of 17-ketosteroids in each of the patients of the premenopausal group in whom repeat studies were available after therapy. The average increase in the 5 patients was 2.5 ± 0.55 mg. in twenty-four hours, which is highly significant. Three of the values after treatment were within the range of normal excretion (cases 6, 8, 15).[2]

TABLE 3. THE AVERAGES OF THE SERUM ELECTROLYTES BEFORE AND AFTER THERAPY

	Before treatment mEq./L	After treatment mEq./L	No. of patients
Sodium	136.4	140.7	7
Chloride	101.1	99.8	6
Potassium	5.15	4.6	4

In the menopausal females, results of excretion were available in 23 cases before treatment, the average being 2.3 ± 0.30 mg. in twenty-four hours. The individual values were considerably below normal range. Several were in the range of excretion found in panhypopituitarism (Cases 5, 18, 25, 29), and in only 3 were the values normal (Cases 28, 37 and 42). Repeat studies were available in 12 cases of this group (*see* Table 2). In 9 of these there was an increased excretion, the average being 1.1 mg; in 3 there was a decreased excretion. The average change in excretion for the whole group was an increase of 0.5 ± 0.35 mg. in twenty-four hours, which is not statistically significant. Only 1 patient (Case 31) of the entire follow-up group had a normal value after treatment. Patient #28, who had no initial determination, had myxedema for ten years and had been off thyroid for one year when first seen. Clinically, she was considered to be a "mild case." One patient (Case 43) was not included in the above averages because of the likelihood that she had Addison's disease in addition to myxedema.

Serum electrolytes and salt restriction. The averages of serum electrolytes made at the time of original admission were: sodium, 139 milliequivalents per liter in 20 patients; chloride, 97.6 milliequivalents per liter in 14 patients and potassium, 4.76 milliequivalents per liter in 6 patients. The serum

[2] A fourth patient (Case 39), in whom myxedema developed after thyroidectomy, had a normal value after three months of treatment.

electrolytes of the small group of patients followed before and after therapy are shown in Table 3. The values are similar to those first mentioned for the larger group. After therapy there was a slight rise in serum sodium and a slight fall in serum chloride and potassium.

TABLE 4. THE CUTLER-POWER-WILDER TEST IN CASE 4 ON ADMISSION AND AFTER THREE MONTHS OF THYROID THERAPY

	Before treatment				After treatment			
	Blood mEq./L		Urine mEq./L		Blood mEq./L		Urine mEq./L	
	Initial	End	24 hr.	4 hr.	Initial	End	24 hr.	4 hr.
Sodium	126.0	120.5	75.0	59.3	140.1	139.5	10.3	0.44
Chloride	94.0	87.0	56.0	51.0	102.0	102.0	21.0	16.0
Potassium	4.2	5.3	82.6	58.2	5.1	5.1	75.0	36.3

Cutler-Power-Wilder salt restriction studies were done in 7 patients. The serum electrolyte changes and the excretion of sodium and chloride were normal in 5 cases before and after therapy (Cases 1, 2, 3, 5, 6). In Case 4, however, before therapy the serum sodium and chloride dropped to levels found in true Addison's disease and the 24-hour sodium and chloride excretion were likewise in the Addison's disease range (Table 4). The 4-hour excretion of these electrolytes, although not as marked as in complete hypoadrenocorticism, was well beyond normal limits. On the third morning of the test, symptoms of crisis developed, with nausea, vomiting and abdominal pain. The blood pressure did not drop. Following three months of thyroid therapy, the results of initial serum electrolyte determinations and of salt restriction studies were completely normal (Table 4). The patient had no untoward symptoms or signs during the test. To our knowledge, such a response and recovery in a myxedematous patient has not been previously published. The results of the electrolyte studies in Patient #43, who, we believe, had myxedema and possibly Addison's disease as well, are recorded in the case summary.

Three additional tests were employed to measure the functions of the adrenal cortex, particularly that portion which is concerned with the so-called "S" hormone, namely, the urinary excretion of 11-oxycorticosteroid-like substances, the response of the circulating eosinophils to adrenalin and the insulin-tolerance test.

11-Oxycorticosteroids. The urinary excretion of 11-oxycorticosteroid-like substances was low in all cases but within the lower limits of normal in

Cases 2 and 28. Following therapy, the excretion was even lower in 2 cases, and rose to normal levels in the third (Table 5). The significance of these changes is not known.

Response of eosinophils to adrenalin. The response of the circulating eosinophils to adrenalin, in the presence of a functioning pituitary, should likewise be an index of 11-oxycorticosteroid substances (Table 6). It should be noted that in Case 5, the initial count was made with eosin solution as the diluent rather than with phloxine, and this may account

TABLE 5. THE EXCRETION OF 11-OXYCORTICOSTEROIDS IN THE URINE BEFORE AND AFTER THERAPY

Case No.	Before treatment mg./24 hrs.	After treatment mg./24 hrs.
2	0.21	0.090
4	0.06	0.029
14	0.06–0.12	0.413
28	0.20	—
30	0.13	—

TABLE 6. THE RESPONSE OF THE CIRCULATING EOSINOPHILS TO ADRENALIN (0.35 MG./SQ.M. BODY SURFACE) BEFORE AND AFTER THYROID THERAPY

Case No.	Eosinophils at start, cells/cu. mm.	Per cent drop	Treatment period (yrs.)	Eosinophils at start, cells/cu. mm.	Per cent drop
1	462	46	7/12	453	36
2	186	63	7/12	181	72
3	427	50	—	—	—
4	379	46	3/12	214	40
5	50*	94	22/12	196	60
6	259	45	3	195	44

* Eosin solution as diluent.

for the low figure. In general, the initial counts were somewhat higher than normal. The average, including Case 5, was 294 cells per cubic millimeter. The per cent drop in eosinophil count after adrenalin was on the borderline of normal in 4 cases (Nos. 1, 3, 4 and 6) and normal in the other 2. After therapy the initial counts were somewhat lower, the average being 276 cells per cubic millimeter. The per cent drop in eosinophils after adrenalin was low-normal in Cases 1, 4 and 6, and normal in the other 2.

Insulin-tolerance tests. The percentage change in blood sugar after

intravenous insulin, before therapy with thyroid, is shown in Figure 1. The results are compared with the average normal response obtained by Fraser *et al.* (8). It seems that myxedema produces a curve showing apparent insulin resistance and hypoglycemia unresponsiveness. This has also been shown by others (8). Following therapy the curves, as shown in Figure 2, conform more nearly to the normal. This figure also shows for comparison representative curves from cases of Addison's disease and panhypopituitarism, as obtained by Fraser *et al.* (8).

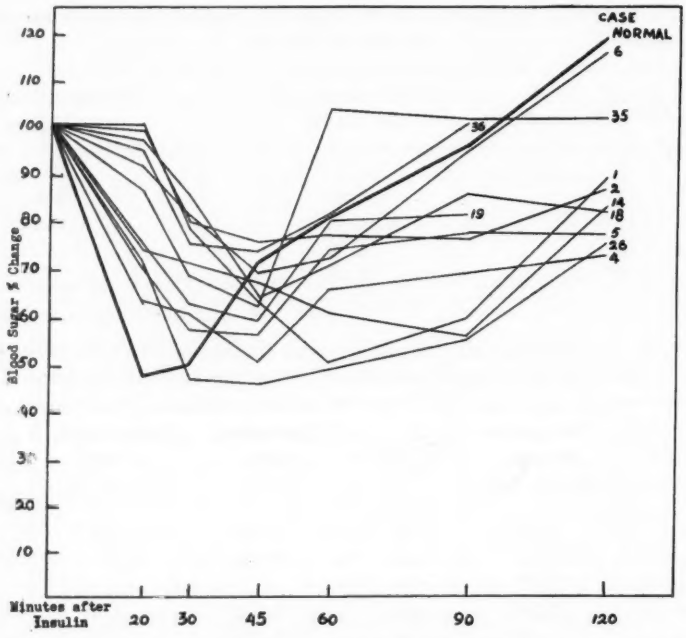

FIG. 1. Insulin-tolerance tests—before therapy. (Curve for the normal response taken from *Fraser et al.* (8).)

Follicle-stimulating hormone. The excretions of follicle-stimulating hormone were determined because of their great value in distinguishing between primary and pituitary myxedema and because their variation might reflect the effect of myxedema on the entire pituitary and on the pituitary-adrenal axis. The urinary follicle-stimulating hormone excretions of the males and premenopausal females were generally within the normal range of 6.5 to 13 mouse units per twenty-four hours (Table 1). In Case 4 in the male group and Case 6 in the female group the results originally were negative for 6.5 mouse units but after therapy with thyroid became

positive for 6.5 mouse units. In addition, the follicle-stimulating hormone excretion in Case 1 became positive for 13 mouse units after treatment, whereas before treatment it was positive only for 6.5 mouse units. On the other hand the follicle-stimulating hormone assay in Case 8 became negative for 13 mouse units after treatment but was positive up to 13 mouse units before treatment. These variations are probably of no significance. Of especial interest is Patient #30, a 41-year-old female, who had not

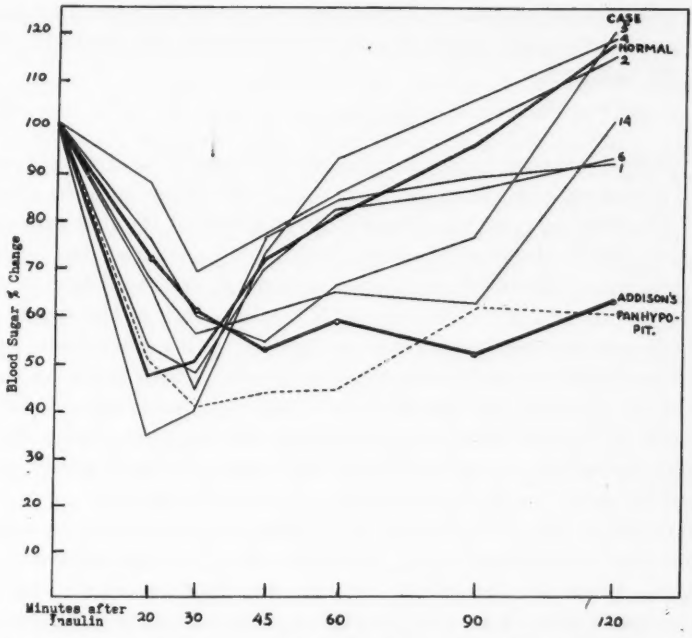

FIG. 2. Insulin-tolerance tests—after thyroid therapy. (Curves for the response in normal subjects, in Addison's disease and in hypopituitarism, taken from *Fraser et al.* (8).)

menstruated for two years. Because the follicle-stimulating hormone assay was negative for 6.5 mouse units, a tentative diagnosis of pituitary myxedema was made. After two months of thyroid therapy, the menses resumed and she has had normal, regular menstruation for several years since. This is not an uncommon occurrence in ordinary myxedema.

In the menopausal group there generally seems to be a somewhat lower level of follicle-stimulating hormone production than the expected high levels of over 104 mouse units found in normal subjects. Before therapy, this is seen in Cases 12, 13, 14, 18, 23, 27, 35, 41 and 43; after

therapy it is apparent also in Cases 7, 12, 18, 27, 31, and 43. Of especial interest are Cases 14 and 19. In the former there was an increase in titer of 2 dilutions after thyroid therapy; in the latter there was an increase of 4 dilutions, from negative for 6.5 mouse units to positive for 104 mouse units.

To summarize—of the total series, 17 patients had follicle-stimulating hormone studies before and after thyroid therapy. Of these, 7 (Cases 1, 4, 5, 6, 14, 19 and 43) showed an increase in titer of one or more dilutions. Two (Cases 7 and 8) showed a decrease in titer of one dilution. In 8 patients studies were not complete and therefore inconclusive (Cases 9, 10, 12, 15, 18, 24, 27 and 31).

DISCUSSION

The interpretation of functional studies of one gland as it affects another is always confused by the possibility that such effects may be mediated through the pituitary, rather than by direct action of the first hormone on the second gland. However, it seems justifiable to assume that since thyroxine has metabolic effects on tissues in general, it should have a similar effect on the adrenal gland as a tissue. Therefore, lack of thyroxine should produce a myxedematous adrenal as well as a myxedematous skin or heart. The variety of possible modes of action is evident when we consider that lack of thyroxine will cause the pituitary to compensate by increased production of thyroid-stimulating hormone, but may also make the pituitary myxedematous. A metabolically depressed pituitary would produce less ACTH, with resultant depression of adrenal function.

This factor of metabolic depression of glands can probably be identified by observing improvement in function after the individual is made euthyroid. However, the effects of long-standing metabolic depression might be irreversible. This complicated interrelationship is further confused by the possibility that partial hypopituitarism may exist independently of hypofunction caused by myxedema. In these cases, if such exist, return to the euthyroid state would not change the measurable level of function of the pituitary gland or those glands stimulated by it.

In interpreting the relation of myxedema to adrenocortical function, one must be aware of the fact that panhypopituitarism often produces concomitant myxedema and hypoadrenocorticism. In these cases it would seem to be impossible to define the direct effect of the two subject glands on each other. Certain clinical features often help in differentiating this type of myxedema from primary myxedema (9) (10), but the distinction is sometimes exceedingly difficult to make.

The foregoing data for this small series of cases permit comment on a few points of interest.

Adrenal androgen or "N" hormone function. Our findings seem to verify the reports of others that the 17-ketosteroid excretion is decreased in the myxedematous patient, and it appears that the decrease is often, but not always, somewhat lower in the menopausal woman than in the premenopausal woman. It may be less marked in early cases than in long-standing cases. This depression of androgens is due mostly to depression of the adrenals, at least in females, but may also be due in part to depression of the luteinizing hormone of the pituitary which is said to stimulate the adrenals to produce androgens. Previous reports suggest that there is no return to normal in 17-ketosteroid excretion after thyroid therapy, except in those with recent post-thyroidectomy myxedema. However, our results indicate that after therapy in the premenopausal woman there tends to be a return to a normal excretion of 17-ketosteroids in most instances, whereas this occurs in the menopausal woman and in males only occasionally. The degree of recovery of function, with a few exceptions, is independent of the amount and duration of therapy. Since thyroid often fails to restore the normal excretion of 17-ketosteroids, it may be considered that thyroid therapy does not represent complete substitution in cases of myxedema of long standing.

Adrenal electrolyte or "Na-K" hormone function. The studies relative to this hormone indicate that its function was essentially normal in all but 1 case. Although the serum sodium concentration was in the low-normal range, the concentrations of serum chlorides and of potassium were not significantly altered. One patient (Case 4) showed marked depression of the electrolyte hormone resulting from long-standing, untreated myxedema but prompt reversion to normal occurred after only three months of thyroid therapy. Deane and Greep's (11) findings that the pituitary in the rat has no direct control of the adrenal glomerulosa, which produces the electrolyte hormone in these animals, might possibly explain the difference in recovery of this hormone as compared to the "N" hormone. The Addisonian response of this patient to the Cutler-Power-Wilder test would tend to refute the contention of Byrom (12) and of others that the sodium held in myxedematous tissue helps to prevent sodium depletion.

Adrenal corticosteroids or "S" hormone function. The data obtained on this function of the adrenal are not sufficient for definite conclusions. The 11-oxycorticosteroid excretion was depressed in all of our patients but was not always below the normal range. The eosinophil counts were generally higher than normal but the response to adrenalin, although in the lower limits of normal, did not indicate any abnormality. The insulin-tolerance tests suggested insulin resistance and hypoglycemia unresponsiveness, as seen in impaired adrenocortical function. However, other mechanisms may explain these abnormalities. For example, the slow circu-

lation and transport of sugar, resulting in diminished utilization of sugar and glycogenolysis, could account for the abnormal insulin-tolerance tests. In any case the results of these tests return to normal after thyroid therapy. It might be conjectured that the response of myxedematous patients to an alarming stimulus would be less than optimal, and if the insult were great enough, might warrant adrenocortical replacement therapy.

Pituitary gonadotropins. It is evident from the studies made on the excretion of follicle-stimulating hormone that metabolic depression of the pituitary may occur. One may therefore surmise that adrenal function may thus be indirectly depressed. The results also demonstrate that pituitary function may improve following replacement with thyroid, as measured by an increase in follicle-stimulating hormone titer. An important corollary of these findings is that complete reliance cannot be placed on follicle-stimulating hormone titer as a means of distinguishing between primary and pituitary myxedema in a woman with amenorrhea, since a negative follicle-stimulating hormone value in such a patient may become positive after thyroid therapy.

It is difficult to find in the literature cases of adrenal cortex atrophy associated with myxedema of thyroid origin. According to Kreibig (13) such patients have been described by Falta and by M. B. Schmidt. Querido (14) has seen such a case which came to autopsy, and one of us (H.S.) has recently seen a marked example of this condition which will be reported at a later date. The reports in the literature deal, for the most part, with patients with Addison's disease and abnormal thyroid histology, namely, diffuse infiltration with lymphocytes, often showing follicle formation with germinal centers, slightly atrophic acini often devoid of colloid, and some increase in fibrous tissue. In most of the reports it is not clear whether or not the patients were clinically myxedematous. Shaw and Smith (15) report 1 such case as a Riedel's struma (probably Hashimoto's struma) associated with Addison's disease. The patient in Brenner's Case 1 (16) was not myxedematous, and in Case 2 showed minimal changes in the thyroid gland. Kreibig's (13) 2 cases showed these changes, the second being less pronounced. Kohler's (17) Case 1 presented the pathologic changes described. In Wells' (18) Cases 2, 3, 4, 5 and 6 there were concomitant adrenal and thyroid changes. However, in Cases 2, 3 and 6 the condition of the pituitary was not stated, so that panhypopituitarism could not be excluded. The cases reported by Weller (19) and by Saphir and Binswanger (20) showed fewer changes in the thyroid, and the case reported by Foster and Barr (21) had questionable pathologic changes in the adrenal. Our own Case 43 is probably an example of Addison's disease in association with myxedema. The laboratory tests indicate some pituitary function.

SUMMARY AND CONCLUSIONS

From our study of the individual cases of this series, it seems possible to group myxedema into five types as regards its relationship to the pituitary and adrenal gland function:

1. Primary myxedema—unassociated with dysfunction of either the pituitary or adrenal. This occurs, apparently, only in recent post-thyroidectomy cases or in idiopathic cases of recent onset.
2. Primary myxedema with secondary depression of adrenocortical function. This depression almost always involves the androgenic hormone, possibly involves the corticosteroids, and occasionally involves the electrolyte hormone. A patient with involvement of all three hormones is represented by Case 4 of the present series.
3. Primary myxedema with secondary depression of the pituitary function. This depression may result in diminished follicle-stimulating hormone excretion in menopausal women, and in amenorrhea in premenopausal women. The possibility that depression of adrenal function in the preceding group is by way of the pituitary must be considered.
4. Primary myxedema and Addison's disease with normal pituitary function, as first suggested by Falta and by Schmidt. This type may be represented by Case 43 of the present series.
5. Pituitary myxedema—as described by Means, Hertz and Lerman and later by Lerman and Stebbins, in which both the thyroid and adrenal fail, secondarily to hypopituitarism.

It should be emphasized that the first three categories represent one clinical group.

Acknowledgment

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PROTOCOLS

Case 4, F.S., (M.G.H. 646176), a 36-year-old single male was first seen in December 1948 because of asthma and fatigue of many years' duration. The fatigue had become of such degree in the previous two years that he had given up his work as a sheetmetal worker. In the last year there had been some epigastric distress or fullness, relieved by soda, eating and walking. A gastro-intestinal x-ray series done elsewhere had shown nothing abnormal.

He had always been intolerant of cold, never perspired, and his skin had always been dry. He shaved about every three days because his beard grew slowly. He had first become aware of short stature at about the age of 12. The other members of his family were all taller than he. He showed little interest in girls and had few other outside interests. There was some recent decrease in libido.

On physical examination, he was found to be intelligent, cooperative and appeared

younger than his stated age. His height was 5 feet, 1½ inches. The hair was dry, lusterless and showed slight temporal recession. The skin was extremely dry and was flaky over the arms and legs. Skin about the eyes was puffy and wrinkled and the facial hair was sparse; pubic and axillary hair was normal. The thyroid was not palpable. The blood pressure was 110/70. The chest was moderately emphysematous, with a few asthmatic breath sounds over all lung fields. The abdomen and genitalia were normal.

Roentgenograms showed a normal sella turcica and union of the epiphyses of the long bones and iliac crests; a bismuth series showed a normal gastro-intestinal tract. The laboratory studies are recorded in Tables 1, 4, 5 and 6, and Figures 1 and 2. There was depression of 17-ketosteroid, follicle-stimulating hormone and 11-oxycorticosteroid excretion. During the Cutler-Power-Wilder test abdominal pain, nausea and vomiting developed, with a marked drop in blood sodium and excessive chloride excretion. These findings are indicative of adrenal insufficiency with respect to the electrolyte hormone.

He was discharged from the hospital with instructions to take 120 mg. of thyroid daily, which he took for three months, and 3 Gm. of sodium chloride daily, which he took for the first month only. On his return to the hospital, he was much improved in every respect. He had considerably more pep and energy, his skin was smooth and only the skin on his legs remained dry. There was a luster to his hair, he was more alert, and the puffiness about the eyes was gone. Even the asthma was much improved. His basal metabolic rate at this time ranged from minus 8 to plus 18 per cent. Further laboratory studies are recorded in the foregoing tables and figures. The Cutler-Power-Wilder test this time gave a completely normal result, and he was free from nausea or abdominal pain during the test.

Comment. The diagnosis in this case was primary myxedema which had probably started in the prepubertal period, and accounted for his failure to grow. The normal sexual development and the measurable quantities of follicle-stimulating hormone indicate that the myxedema was not secondary to hypopituitarism. The insulin-tolerance test was not characteristic of hypopituitarism. Although the eosinophil response was indicative of "S" hormone deficiency, the fact that the patient had asthma may have altered the response. The 17-ketosteroid and 11-oxycorticosteroid excretion did improve after three months of therapy; however, results of the salt deprivation test reverted to normal. A positive Cutler-Power-Wilder response in a patient with primary myxedema has not been previously reported in the literature. As was pointed out in the discussion, the possibility of a myxedematous pituitary producing this picture of adrenal insufficiency must be considered.

Case 43, H.S. (M.G.H. 512466), a 41-year-old married housewife, entered the hospital in November, 1945, for regulation of her "Addison's disease." Nineteen years before entry she had had an unexplained loss of 33 pounds in weight in seven months, with weakness and anorexia. Three years later she became pregnant and had an uneventful delivery which was followed by marked weakness, anorexia, epigastric discomfort and gradual loss of axillary and pubic hair. Menses continued to be regular. Accentuation of these symptoms caused hospitalization, Addison's disease was diagnosed, and she was given desoxycorticosterone acetate injections regularly up to her present admission. Six years prior to admission she noted the onset of dryness of the skin, hoarseness, puffiness of the face and difficulty in thinking. The menopause occurred four years before entry, at the age of 37, and she had "hot flashes" for three years subsequently.

On physical examination, she appeared to be older than the stated age, her face was puffy, and it was mottled by patches of pigmentation. The skin was dry and cool and the hair was coarse. There was no axillary or pubic hair. Blood pressure was 106/76.

The laboratory studies are recorded in Table 1. While in the hospital the desoxycorticosterone acetate was stopped and an acute febrile illness developed, during which the serum sodium dropped to 110 milliequivalents per liter. Desoxycorticosterone acetate was resumed and thyroid was also administered. She soon began to feel better and experienced the onset of libido for the first time in years. Desoxycorticosterone pellets were implanted and she was discharged taking thyroid, 45 mg. daily, by mouth.

Six months later, while still being treated with desoxycorticosterone pellets, a Kepler test gave positive results in part I and negative in part II. The Cutler-Power-Wilder test showed a chloride excretion of 42 milliequivalents per liter during the four-hour period. At the end of the test, serum sodium was 133 milliequivalents per liter and chloride 102 milliequivalents per liter. Although this is a normal result, its value in the presence of therapy with desoxycorticosterone acetate pellets is questionable. An insulin-tolerance test showed a normal curve of 74, 28, 30, 44, 52, and 71 milligrams per cent.

In May, 1949, desoxycorticosterone pellets were not implanted and the patient was maintained on 5 mg. of methyltestosterone daily, 3 Gm. of sodium chloride daily and 100 mg. of thyroid daily. She continued to do well until her reentry for further study in January, 1950. On examination at this time, the skin was less dry and the hair was of normal texture. Pigmentation was still present on the face but somewhat less marked than originally. There was no pigmentation of the mucous membranes. The ear cartilages were found to be rigid, the patient having noted this herself in the last few weeks. Blood cholesterol was 214 milligrams per cent. Other laboratory tests are recorded in Table 1. The eosinophil count was 35 cells per cubic millimeter, and four hours after 25 milligrams of ACTH it was 58 cells per cubic millimeter, thus showing no response. The uric acid/creatinine ratio showed a rise of 4.6 per cent and the potassium/creatinine ratio a rise of 47 per cent, indicating failure of adrenal response. The Cutler-Power-Wilder test showed a chloride excretion of 92 milliequivalents per liter and a sodium excretion of 99.2 milliequivalents per liter in the four-hour period—a positive result. The excretion of follicle-stimulating hormone was positive for 13 units and questionably positive for 52 units, which is unusually low for the menopause.

Comment. The onset of myxedema several years before the menopause and the marked general improvement during therapy, favored the diagnosis of primary myxedema rather than pituitary myxedema. Although the diagnosis of Addison's disease was not established beyond a doubt, the clinical course and laboratory studies seemed to point to this diagnosis. The generalized improvement in physical condition after therapy was not paralleled by the salt restriction test, as in Case 4. Addison's disease with pigmentation is not ordinarily found to this degree as a result of panhypopituitarism. However, the absence of pigmentation in the buccal mucosa might favor the latter diagnosis. Depression of pituitary function was evident in the low follicle-stimulating hormone excretion associated with the menopause, but the history of "hot flashes" and the improvement in follicle-stimulating hormone titer during thyroid therapy were in favor of a functioning pituitary. We, therefore, believe that this patient probably represents both primary athyreosis and primary adrenal cortical insufficiency, with a normal, although functionally depressed, pituitary.

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SIMMONDS' DISEASE

REPORT OF A CASE OBSERVED FOR NINE YEARS, WITH POSTMORTEM FINDINGS

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FOR a decade following Simmonds' report (1) of the syndrome bearing his name, many cases were recorded as Simmonds' disease which were not proven at autopsy. Excellent clinical reviews by Silver (2), Calder (3), and Escamilla and Lisser (4) revealed that most of the cases that had been reported as Simmonds' disease were in reality instances of anorexia nervosa. Of 595 case reports reviewed by Escamilla and Lisser (4) in 1942, there were 101 verified cases of Simmonds' disease. Additional verified cases have been reported by Robertson (5), Darley (6), and Beare (7). Because of the relatively few proven cases in the literature, the following confirmed case is reported.

CASE HISTORY

B.C., a 28-year-old white primipara, was first admitted to Saint Louis City Hospital in 1935 because of toxemia of pregnancy. At the age of 9 she had had scarlet fever which she did not recall as eventful and at no other time had she experienced any serious illness. Following several mild convulsions, cesarean section was performed and a living baby was delivered at six and one-half months' gestation. The patient was discharged from the hospital one month later with an albuminuria of 1 plus and a blood pressure measuring 124/92 mm. Hg.

Sixteen months later she was re-admitted for a normal spontaneous delivery. Her third pregnancy terminated in a spontaneous miscarriage at three months' gestation.

She again entered the hospital in a pregnant state in January, 1939, relating that she had experienced a convulsion the day before. The blood pressure measured 140/120 and there was 4 plus albuminuria. Eleven days after entrance she had a spontaneous delivery. Immediately following delivery she suffered from shock and the blood pressure was recorded as 60/30. Special notation on the record indicated that blood loss during parturition was not remarkable. For the first time, unusual dryness and pallor of the skin was noted. The basal metabolic rate, estimated for the first time, was found to be minus 26 per cent. On the thirteenth postpartum day the patient became confused and disoriented and was believed to be suffering from postpartum psychosis. After one month, the patient was removed to Saint Louis City Sanitarium for special psychiatric

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treatment. After six months in this institution she was discharged as having recovered. During her stay in the Sanitarium a basal metabolic rate determination was minus 41 per cent, and desiccated thyroid was prescribed in sufficient amounts to elevate the rate to minus 10 per cent. Thyroid did not improve the dryness of the skin or other manifestations of hypothyroidism.

In June, 1940, six months after her last delivery, she was again admitted to City

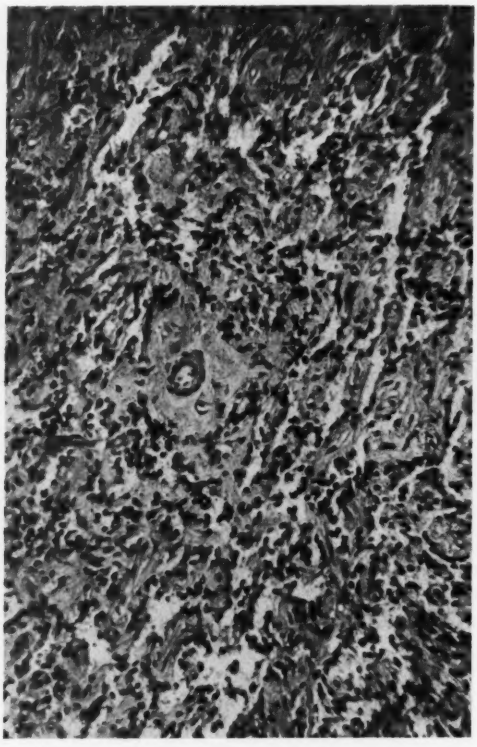

FIG. 1. The central portion of the anterior pituitary gland. Anterior lobe cells are atrophic or absent, and there is a relative increase in connective tissue and stromal vessels (hematoxylin-eosin stain; ×300 approx.).

Hospital with complaints of nervousness, weakness, absence of menses since onset of the previous conception twenty-seven months before, and anorexia with weight loss of twenty pounds. She was extremely reticent and negativistic. There was marked dryness of the skin, advanced dental decay, absence of pubic and axillary hair, and atrophy of the breasts. Vaginal examination by Dr. Willard Allen showed the vaginal mucosa to be thin and the fundus to be unusually small. The average of five basal metabolic estimations was minus 34 per cent. Other laboratory studies done at this time gave the following results: *urinalysis*, 1 plus albumin; *hemoglobin*, 70 per cent; *red blood cell count*, 3.19 million; *white blood cell count*, 4,800; *differential count*, normal (3 per cent eosinophils);

fasting blood sugar, 49 to 58 mg. per cent; *sugar tolerance test*, fasting 57 mg. per cent, 30 minutes 70 mg. per cent, 60 minutes 96 mg. per cent, 120 minutes 37 mg. per cent, 240 minutes 55 mg. per cent; *insulin tolerance test*, fasting 55 mg. per cent, 15 minutes (after 5 units of insulin) 51 mg. per cent, 30 minutes 42 mg. per cent, 45 minutes 39 mg. per cent, 60 minutes 37 mg. per cent; *nonprotein nitrogen*, 20 mg. per cent; *total serum protein*, 7.71 Gm. per cent with an A/G ratio of 1:39; *serum cholesterol*, 267 mg. per cent. There was no *free hydrochloric acid* in the gastric secretion. The *electrocardiogram* showed low voltage throughout with bradycardia (rate 46) and inverted T waves in leads

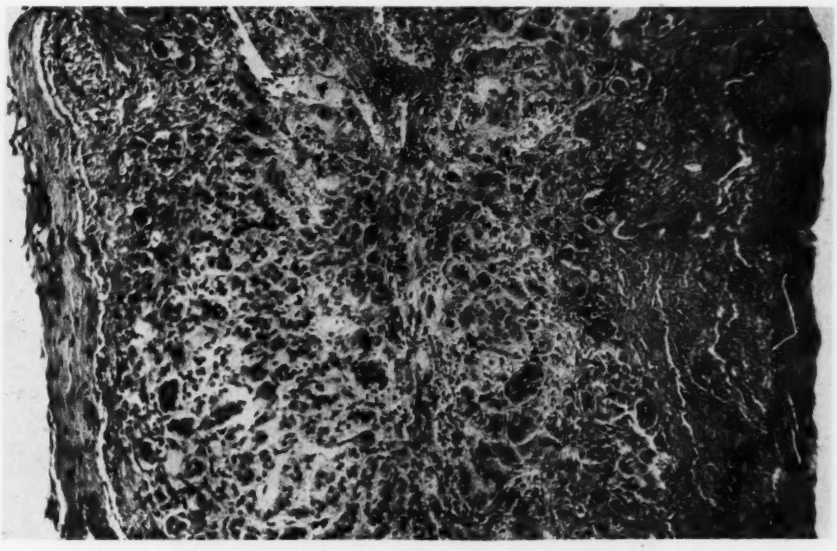

FIG. 2. The full thickness of one adrenal gland. There is marked atrophy and loss of lipoid of all zones of the cortex, and thickening of the capsule. A tributary of the central vein is seen at the top. The medulla does not appear in the section (hematoxylin-eosin stain; ×150 approx.).

1 and 3. *X-ray* examination of the lateral skull showed a normal sella turcica. *X-ray* study of the chest showed nothing abnormal. The diagnosis of Simmonds' disease was made tentatively.

Treatment included desiccated thyroid, adrenal cortical extract, desoxycorticosterone, stilbestrol, testosterone propionate, and sodium chloride, given separately and in combination for a period of ten weeks. Although improvement was not dramatic, it was definitely established that most benefit was derived from the adrenal cortical extract. On this admission, after a hospital stay of three and one-half months, the patient was discharged very much improved and advised to take 10 grams of salt daily.

She was re-admitted six months later for the fifth time and during the following seven years she had eight additional admissions, the final one being in January, 1948. Most of the admissions were for weakness and hypoglycemic attacks. During 1946 she was admitted during an Addisonian crisis which responded to adrenal cortical extract and

saline and glucose infusions. Following this episode, desoxycorticosterone acetate pellets were implanted and periodic implants followed thereafter.

Her final entrance was in January, 1948. She had become markedly depressed and lapsed into a negativistic state. Attempts to spoon-feed her were not too successful and she lost weight rapidly. She was given additional adrenal cortical therapy. She had numerous hypoglycemic reactions that required repeated glucose infusions. After two

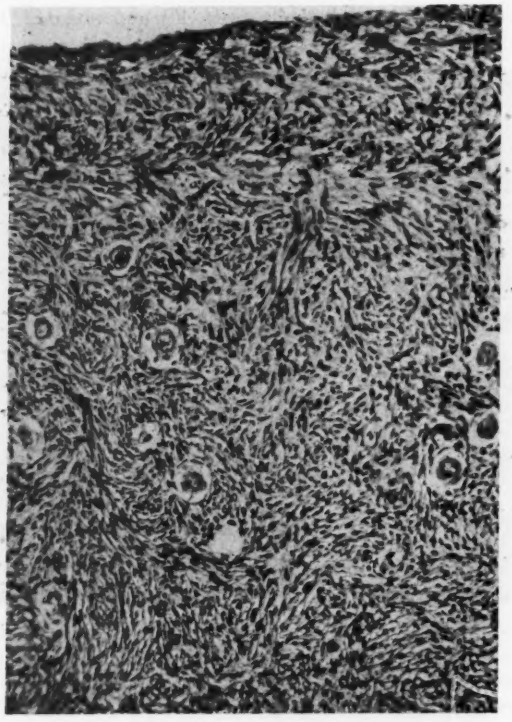

FIG. 3. Section from one ovary, showing well preserved primordial follicles (hematoxylin-eosin stain; ×150 approx.).

months she was considered physically able to withstand electric shock therapy which had been recommended by the consulting psychiatrist. Following 20 electric shock treatments over a period of six weeks, she was improved mentally. Severe hypoglycemic episodes continued and in spite of intravenous glucose and saline and adrenal cortical extract, she lapsed into a semistuporous state and could be aroused only with difficulty. Shortly before death her weight was 94 pounds, which was a loss of 40 pounds (30 per cent) over her average weight.

On June 17, 1948, six months after the date of the last entrance, she expired. This was at the age of 41, nine years after the onset of symptoms.

A postmortem examination was made, with the following findings:

The body appeared extremely emaciated. The hair of the head was sparse, as was axil-

lary and pubic hair. The breasts were small, with prominent pigmentation of areolae. The external genitalia appeared somewhat atrophic.

The *thyroid* and *parathyroid* glands were not grossly identified, although a careful search was made. In one of eight pieces of tissue removed from the thyroid region was a small area of lymphocytes which contained a few large epithelial cells in acinar arrangement, presumably a remnant of the thyroid gland (Fig. 1). In other sections were areas

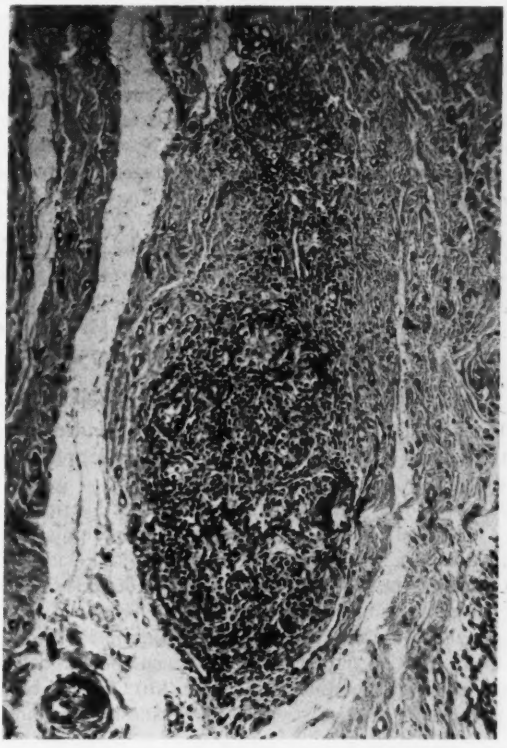

FIG. 4. Tissue removed from the location of the thyroid in the neck. Several small groups of epithelial cells in acinar arrangement are seen associated with an infiltration of lymphocytes. No colloid is present (hematoxylin-eosin stain; ×150 approx.).

of dense fibrosis, numerous foci of lymphocytes, an occasional small deposit of calcium and one parathyroid gland, measuring 2×1 mm. in microscopic section. The parathyroid gland was located next to loose fibrous tissue and was composed of rather thick cords of small chief cells supported in a moderately vascular stroma.

The *pancreas* was small, firm, tan and lobulated. The acinar tissue was not remarkable, but the islets, although present in usual numbers, were composed of relatively small cells with small, round, deeply staining nuclei.

The *adrenal glands* were extremely small, the left and right weighing 1.0 and 1.1 Gm., respectively. The cortex was markedly thin and made up of short columns of small cells

containing a few vacuoles in the cytoplasm (Fig. 2). The medulla was demarcated from the cortex by a zone of loose fibrillar tissue. The cells of the medulla were not unusual.

The *uterus* was small, measuring 6.5×4.2×3 cm., and the uterine wall was 1.2 cm. in thickness. The *ovaries* were also small and no corpus luteum was seen in either ovary. The myometrium was composed of small muscle cells and moderate hyaline fibrous tissue. The endometrium was made up of glands lined with columnar epithelial cells in a compact fibrillar stroma. Some of the endocervical glands were lined with columnar cells having nuclei which varied in size and staining properties, possibly a response to the administration of estrogenic and other hormones. In the ovaries were moderate numbers of primordial follicles (Fig. 3). The granulosa of several follicles was moderately well developed. One follicle had reached the stage where the central portion had become cystic, and there was beginning degeneration of the granulosa layer. Other small cystic structures were present which resembled follicles undergoing atresia after growth to about 1 mm. in diameter. Numerous corpora albicantia in all stages of regression were seen.

The *pineal gland* appeared slightly enlarged, weighing 180 mg. It contained a few concretions.

The *pituitary gland* was small, weighing 120 mg. It consisted of a yellow portion and a gray-white portion, measuring 3 mm. and 1.5 mm., respectively, in antero-posterior dimensions. Dense fibrous tissue appeared to compress and distort the anterior lobe into small groups and thin strands of anterior lobe cells (Fig. 4). Many of the cells were small, and in these the nuclei appeared pyknotic. A few lymphocytes were seen between the cells. Staining with toluidin blue and safranin revealed most of the cells to be chromophobes; a few eosinophils were identified, but no basophils were seen. A few small round foci of basophilic hyaline material were present. Several small acinar structures filled with colloid were seen adjacent to the pars nevosa, which also appeared compressed and atrophic.

Lymph nodes of the cervical, mediastinal, mesenteric, and peripancreatic regions were enlarged, and the lymphoid follicles of the large intestine appeared prominent. Malpighian bodies of the spleen were large and numerous, and small foci of lymphocytes were scattered throughout the red pulp. Lymph nodes contained an abundance of small lymphocytes, but the germinal centers appeared poorly developed.

Other findings included chronic endocarditis of the mitral and tricuspid valves of moderate degree (heart weight, 260 Gm.), bronchopneumonia and fibrous scars of lung apices, atrophy and passive congestion of the liver (810 Gm.), of the kidneys (150 Gm. together) and of the spleen (100 Gm.), and slight lipoidosis of the aorta.

COMMENTS

During the first years of the total thirteen-year period of observation, there was considerable conjecture as to whether our patient might not have anorexia nervosa. It was during the periods of partial remission that doubt as to the diagnosis of Simmonds' disease arose. The lowered basal metabolic rate and the low blood sugar values with increased sensitivity to insulin were the most significant laboratory aids pointing to the diagnosis of Simmonds' disease. In the very beginning of our patient's illness, signs of myxedema were predominant, but thyroid therapy was not effective; neither was it harmful as far as known. In the later years of illness our patient possessed the characteristics of the typical postpartum

syndrome. Although symptoms of the disease first became evident in 1939 at the time of delivery of the third living child and the fourth pregnancy, it is believed that the illness had its onset with the first pregnancy when toxemia occurred. If this assumption is accurate, damage to the pituitary was only partial. Sheehan (8) has pointed out that undamaged portions of the hypophysis may compensate for portions destroyed, thereby permitting the pituitary to function normally. This theory would explain the three pregnancies that occurred subsequent to the speculated date of onset of this illness. In 1918 Simmonds (9) pointed out that fairly large portions of the anterior pituitary must be destroyed before the symptoms of pituitary failure occur.

Outstanding among the postmortem findings was a small pituitary gland which weighed 120 mg. Fibrous tissue compressed and distorted the anterior pituitary into small groups of cells, comprised chiefly of chromophobes. It is of added interest that there were a few eosinophils, but that no basophils were identified. The profound degree of atrophy of the thyroid gland is evidenced by the fact that the gland could not be identified grossly. Several sections of tissue taken from the thyroid area were examined microscopically. From one of these sections there was evidence of thyroid tissue as demonstrated in Figure 4. The parathyroid glands likewise could not be identified grossly, but definite parathyroid structure was found in a microscopic section made from tissue removed from the parathyroid area. The small adrenal glands were the result of atrophy of all layers of these structures. Atrophy of the uterus and ovaries was advanced, as might be anticipated. The loss of end-organ function which this patient experienced was readily explained by the postmortem findings, which fulfill the requirements for the diagnosis of Simmonds' disease.

SUMMARY

A verified case of Simmonds' disease is reported in a white female in whom symptoms first occurred at the age of 32, during her fourth pregnancy. She had suffered from toxemia of pregnancy during the first pregnancy, four years previously, which seemingly dates the onset of the illness. Psychic disturbances with hallucinations were present. The most disturbing organic disorder was hypoglycemia. Adrenal cortical extract together with glucose and saline infusions offered most in the way of treatment.

Death finally came during a severe hypoglycemic attack nine years after the onset of symptoms and when the patient was 41 years of age. Postmortem examination revealed atrophy of the adenohypophysis, thyroid, adrenals, and ovaries.

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THE RADIOIODINE-ACCUMULATING FUNCTION OF THE HUMAN THYROID GLAND AS A DIAGNOSTIC TEST IN CLINICAL MEDICINE*

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HAMILTON and Soley (1, 2) were the first to observe that the thyroidal accumulation or urinary excretion of ingested radioiodine could be correlated with the clinical state of thyroid function. It has been apparent from the first that this correlation provided a useful research tool and also a functional test which might have practical clinical value in the diagnosis and management of thyroid disease. The numerous studies of radioiodine in patients which have appeared in the past ten years have involved various methods for evaluating the behavior of radioiodine tracers. The methods employed have included a) various observations of urinary excretion of radioiodine (3–6), b) direct in vivo observations of radioiodine in the thyroid (6–9) and c) estimation of various rates derived from observations of the urine (10, 11), the thyroid (12–15), the serum (16) or a combination of these (15, 17, 18). Comparatively few of the published reports have included enough cases to allow critical appraisal of the diagnostic usefulness and clinical limitations of radioiodine tracer tests. Werner, Quimby and Schmidt (19), employing as their criterion of thyroidal accumulating function the quantity observed in the thyroid twenty-four hours after administration of the dose, have published observations on 269 patients having various conditions. Skanse (5) has reported his observations of radioiodine tracer tests of 110 normal subjects and 385 patients who had various disease conditions, employing as a criterion the quantity of radioiodine excreted in the urine within twenty-four and forty-eight hours after administration of the dose.

No extensive diagnostic studies have yet appeared in which the observations have been expressed as rates. It is our opinion, for reasons dis-

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cussed elsewhere, that the nature of the radioiodine-accumulating function of the thyroid gland is such that it can be evaluated most explicitly and quantitatively by expressing it as a function of time, that is, as a rate. It is the purpose of this paper to present an analysis of radioiodine tracer tests by such methods, and to compare the results observed with those obtained with other technics, including the urinary excretion in the period of forty-eight hours after administration of the dose, as employed by Skanse, and the quantity of radioiodine observed in the thyroid twenty-four hours after administration of the dose, as reported by Werner, Quimby and Schmidt.

MATERIAL AND METHODS

All of the patients on whom this report is based received a "standard" tracer dose consisting of 100 microcuries of I^{131}, with 100 micrograms of NaI^{127} as carrier. This was given by mouth between 8:30 and 9:00 A.M., breakfast having been withheld. In more than 95 per cent of cases the patients were observed as outpatients, and were carefully instructed in the technic for accurate collection of urine samples. In hospitals where this task was generally left to the nursing service, much more difficulty was encountered with collections. The urine was routinely collected at six-hour intervals for the first twenty-four hours, and at twenty-four-hour intervals during the ensuing two days and sometimes longer. In patients suspected of having hyperthyroidism, urine collections were routinely made at two-hour intervals for the first six hours. The technic for analyzing urine has been reported elsewhere (10). In many cases, in vivo observations were made twenty-four and forty-eight hours after ingestion of the tracer, and in a substantial proportion of the cases at much more frequent intervals. The counts recorded over the thyroid were expressed in absolute terms as a proportion of the dose given (13).

In the period from October 1, 1946, through December 31, 1949, radioiodine tracer studies were carried out in accordance with the foregoing routine on 790 patients. When more than one tracer was given to the same person, only the first one was employed in this study. The patients studied during this interval were not selected for study routinely or consecutively. Tracer studies were obtained in as many individuals with as many different clinical conditions as possible in which the test conceivably might have diagnostic usefulness. In addition, data were sought in conditions associated with impaired renal function in order to determine the influence of renal function on the test.

The records of all of the patients were carefully reviewed, and an attempt was made to establish a clear-cut diagnosis with respect to thyroid function and with respect to the major ailment. Such diagnoses

were made according to careful criteria, which will be enumerated subsequently, without regard to the results of the radioiodine tracer study. Particular pains were taken to weed out cases in which the data were known to be technically faulty, and cases in which the final diagnosis with regard to the thyroid gland was questionable, on the basis of evidence which did not include the radioiodine study. Also excluded from consideration in the diagnostic study were 1) all patients known to have received inorganic iodides in therapeutic quantities within three weeks, 2) all patients known to have received propylthiouracil, potassium thiocyanate

TABLE 1. PRELIMINARY CLASSIFICATION OF 790 CASES EMPLOYED IN THIS STUDY

Group	No. of cases	Percentage of total
A. Cases included in diagnostic study		
I. Conditions unassociated with thyroid disease	111	14.2
II. Euthyroid conditions with associated thyroid disease	150	19.0
III. Hyperthyroid conditions	175	22.2
IV. Hypothyroid conditions	93	11.7
V. Miscellaneous conditions	17	2.1
Total	*546*	*69.2*
B. Cases excluded from diagnostic study		
I. Technically faulty data	16	2.0
II. Thyroid diagnosis equivocal	97	12.3
III. Previous treatment with iodine or antithyroid drugs	131	16.5
Total	*244*	*30.8*

or other antithyroid drugs within three months, and 3) all patients known to have received organic iodine compounds, including desiccated thyroid, iodoalphionic acid (Priodax), sodium iodomethamate (Neo-iopax) or iodized oil (Lipiodol) within two years of the test. The preliminary classification of cases is summarized in Table 1.

Excluding all cases in the foregoing categories, there remained 546 cases in which the data were free of known imperfections, the diagnosis with respect to thyroid function was clear and there was no known history of the ingestion of iodine or antithyroid drugs within the time stated. It is from this group of cases that analysis of urinary observations (Table 1) will be made.

Prior to January 1, 1948, urinary data alone were routinely obtained; since that date, in vivo observations also have been made routinely whenever possible. In the case of very sick patients, and sometimes for other

TABLE 2. SUMMARY OF MEAN RADIOIODINE VALUES IN VARIOUS CONDITIONS

Group, number	Condition	No. of cases	Basal metabolic rate, per cent	48-Hour urinary excretion, per cent of dose	Renal fraction, per cent of dose	Disappearance rate, per cent per hour	Renal excretion rate, per cent per hour	Extrarenal disposal rate, per cent per hour	Cases	24-Hour thyroidal accumulation, per cent of dose	Accumulation rate, per cent per hour
A.	Conditions unassociated with thyroid disease										
1.	No abnormal findings on examination	11	− 1.5±3.0*	64.5±1.4	63.8±1.4	11.2±1.0	7.1±0.6	4.1±0.5	5	28.3±4.6	3.0±0.5
2.	Carcinoma, nonthyroidal	7	− 0.9±1.5	55.7±3.0	56.6±4.2	9.9±0.7	5.5±0.4	4.4±0.6	5	32.0±6.9	3.1±0.3
3.	Functional disorders	30	+19.0±2.8	64.0±2.1	63.6±2.2	12.7±0.6	7.9±0.4	4.7±0.4	13	29.0±4.9	3.7±0.7
4.	Low basal metabolic rate without myxedema	11	−22.5±1.5	64.7±1.9	65.4±2.0	9.5±0.6	6.2±0.4	3.3±0.3	9	21.9±3.2	2.1±0.4
5.	Essential hypertension	15	+17.8±2.7	63.3±2.5	64.7±2.3	9,2±0.7	6.0±0.5	3.2±0.2	5	19.6±5.9	1.9±0.5
6.	Heart disease, compensated	8	+21.8±4.1	63.5±4.5	64.5±4.7	8.6±0.6	5.4±0.6	3.2±0.5	6	17.1±4.5	2.2±0.6
7.	Heart disease, decompensated	14	+14.4±2.6	48.5±2.6	53.9±3.2	5.2±0.4	2.8±0.3	2.3±0.2	9	16.6±4.3	1.4±0.5
8.	Renal insufficiency	5	+ 0.3±12.3	45.7±8.8	56.3±9.1	2.1±0.5	1.2±0.2	0.9±0.3	1	26.0–	1.3–
9.	Addison's disease	10	− 7.9±2.6	59.2±4.7	62.3±5.1	7.4±1.1	4.3±0.5	3.1±1.0	1	3.6–	0.7–
B.	Euthyroid conditions associated with thyroid disease										
10.	Malignant thyroid tumors	75	− 0.7±1.3	63.7±1.1	64.5±1.2	10.4±0.3	6.7±0.2	3.7±0.2	55	24.4±1.3	2.9±0.2
11.	Adenomatous goiter without hyperthyroidism	49	− 1.3±1.3	61.2±2.0	61.6±2.1	13.0±0.8	7.7±0.3	5.3±0.6	27	31.8±3.9	4.6±0.9
12.	Colloid goiter	3	+ 3.3±7.8	46.3±7.2	44.9±6.9	13.0±1.0	6.8±1.0	6.2±0.2	2	(36.0) (44.3)	(9.8) (4.9)
13.	Exophthalmos of Graves's disease	23	− 4.5±2.1	63.4±2.7	64.5±1.6	12.3±0.9	7.8±0.5	4.5±0.5	11	23.8±3.5	2.9±0.5
C.	Hyperthyroid conditions										
14.	Exophthalmic goiter	123	+34.2±1.4	25.4±1.3	24.3±1.3	30.9±1.4	5.9±0.2	25.0±1.5	61	63.2±1.5	22.1±2.0
15.	Exophthalmic goiter with cardiac decompensation	20	+34.5±3.0	20.6±3.2	19.3±3.3	28.0±4.8	4.2±0.6	23.8±4.3	6	60.5±6.2	23.7±9.4
16.	Adenomatous goiter with hyperthyroidism	25	+29.7±3.1	42.5±3.6	42.7±3.9	22.4±3.6	7.6±0.7	14.8±3.3	13	47.8±4.4	14.4±4.5
17.	Acromegaly	7	+20.1±3.8	61.7±3.7	62.9±3.7	12.9±1.4	8.0±0.9	4.8±0.7	2	(19.5) (29.8)	(2.0) (3.2)
D.	Hypothyroid conditions										
18.	Myxedema	46	−25.9±1.4	76.7±1.2	81.7±1.2	6.6±0.3	5.4±0.3	1.2±0.2	28	4.8±1.2	0.3±0.1
19.	Hypopituitarism	5	−26.4±6.5	73.2±3.2	76.8±3.4	7.2±1.4	5.5±1.0	1.7±0.4	4	6.8±4.2	0.7±0.5
20.	Acute diffuse thyroiditis	16	+ 5.0±2.2	80.6±2.0	82.3±2.0	9.0±0.6	7.4±0.6	1.6±0.2	10	4.9±2.2	0.5±0.3
21.	Hashimoto's thyroiditis	7	−17.3±4.2	62.9±7.6	63.0±7.8	11.0±1.2	6.7±0.7	4.3±1.2	4	29.8±11.0	4.3±2.0
22.	Riedel's thyroiditis	4	− 8.0±4.8	75.5±4.5	77.0±3.6	8.1±0.9	6.3±3.7	1.8±1.0	3	11.0±5.7	1.0±0.3
23.	Thiocyanate myxedema	15	− 9.9±3.2	72.7±4.1	73.2±4.5	6.8±0.7	4.0±0.4	2.8±0.7	11	18.2±4.2	1.8±0.7

* The values given are the means and standard errors of the mean.

reasons, in vivo observations were not practicable, so that additional cases were obtained in which only urinary data were available. In 300 of the foregoing 546 cases additional in vivo observations were also available for analysis. In order to compare urinary and thyroidal observations directly, both types of data were separately analyzed for this second series of patients. No significant differences were observed between the means and distributions of urinary observations for the entire series of 546 cases and the means and distributions of urinary observations in the 300 of these in which in vivo observations were also made. Accordingly in order to conserve space, Table 2 summarizes the urinary data for the whole series and in vivo data for that part of it in which such were available.

OBSERVATIONS

In Table 2 are summarized urinary observations of radioiodine tracers in 529 cases and thyroidal observations in 291 cases, classified according to diagnosis and compared with the basal metabolic rate. Data on 17 miscellaneous cases not included in Table 2 are given in Table 4. The significance of the rates derived from the urinary excretion curves and thyroidal accumulation curves of radioiodine has been discussed in detail elsewhere (10). The analysis on which the rates are based assumes that initially, and as a first approximation, the excretion of radioiodine in the urine, its disappearance from the blood and its accumulation in the thyroid are related simple exponential functions. Later, radioiodine which has been fixed in tissue, or the thyroid, may re-enter the blood and complicate the relationship. Attempts have been made to develop complex exponential equations which deal with all these subsequent events (18). It is evident from such efforts that no great error results from ignoring subsequent events and determining the initial disappearance of inorganic radioiodide into the urine, the thyroid and the tissues from the initial portions of the urinary or thyroidal curves. In the case of euthyroid persons, the initial curves remain approximately exponential in form for twenty-four to forty-eight hours, in myxedematous patients for four or five days, and in some hyperthyroid patients the initial exponential curve can be followed for only three or four hours. These time relations hold for thyroidal and serum curves as well as urinary observations.

The values listed in Table 2 may be defined as follows: 1) Forty-eight-hour urinary excretion (UE) is the proportion of the dose observed in the urine collected for forty-eight hours after administration of the dose. 2) Renal fraction (RF) is the asymptotic value of the urinary excretion curve; it is the fraction of the total dose which would ultimately appear in the urine if the initial simple relationship continued to obtain. It will be observed that this value corresponds approximately to the observed

UE. 3) Disappearance rate (DR) is the proportional rate at which inorganic radioiodide is disappearing from the blood. 4) Renal excretion rate (RER) is the proportional rate at which inorganic radioiodide is being removed from the blood by the kidneys. This is a measure of renal function with respect to iodide, not a measure of thyroid function, and is included here to indicate whether alterations in renal function influence the behavior of radioiodine in the body. 5) Extrarenal disposal rate (ERDR), termed in our original publication "collection rate" and by Mason and Oliver (11) "thyroid rate," is the proportional rate at which radioiodide is being removed from the blood by all tissues together other than the kidneys. To the extent that the thyroid is the chief of these, it is an index of thyroidal accumulation rate. 6) Twenty-four-hour thyroidal accumulation (TA) is the proportion of the dose observed in the thyroid by in vivo measurements twenty-four hours after administration of the dose. 7) Accumulation rate (AR) is the proportional rate at which inorganic radioiodide is being removed from the blood by the thyroid. Since direct determination of this index would require six or more in vivo observations in each case, several of them during the first day, it is impractical for routine purposes. The values recorded here were obtained by a calculation based on the urinary excretion curve and a single in vivo observation at twenty-four hours. The basis for this procedure and a comparison of accumulation rates determined by the two methods are described elsewhere. In the case of patients who have exophthalmic goiter, accumulation rates calculated by the methods here employed are invariably erroneously low, owing to the time relationships discussed previously. However, the error is great only in very high rates and is negligible in rates in or near the normal range. On this account, accumulation rates calculated in this fashion should be as useful diagnostically as more accurate accumulation rates calculated by the more arduous method of obtaining multiple in vivo observations.

A. Conditions unassociated with thyroid disease

1. Negative results of examination.—This group includes 11 healthy adults (6 men and 5 women; average age 44 years). This is too small a group to fix the normal range in statistical terms; however, when one takes into account the consistent values observed in this and subsequent groups without thyroid disease as well as those observed in the subsequent euthyroid groups (10–13) some idea of the probable normal range may be obtained. The mean values are given in Table 2. These may be compared with the normal range chosen (Table 6) as follows: UE 45 to 82 per cent, ERDR 1.3 to 7.9 per cent per hour, TA 6 to 45 per cent, AR 0.5 to 6.8 per cent per hour.

2. Carcinoma, nonthyroidal.—This category includes 7 persons without evident disturbance of the thyroid who had malignant disease elsewhere in the body. The average age was 54 years; 3 patients were men and 4 were women. All were in fairly good physical condition. The mean UE and RF were both significantly reduced as compared with these

values for group 1; this is evidently due to reduced RER (mean 5.5 per cent per hour) for this group. Other radioiodine values and the mean basal metabolic rate were not significantly different from those of the previous group.

3. Functional disorders.—This group includes 30 patients, 20 women and 10 men, whose average age was 45.8 years. Included are patients who had chronic nervous exhaustion, anxiety tension states and similar conditions, without clinical evidence of any organic disease, especially thyroid disease. Such patients frequently have symptoms resembling those of hyperthyroidism and frequently have elevated metabolic rates. The criteria for selection in this category did not include the basal metabolic rate but rather absence of clinical or laboratory evidence of organic disease, the presence of a normal thyroid gland by palpation, and complete absence of objective signs of hyperthyroidism or hypothyroidism. None of the seven radioiodine values obtained from I^{131} studies differed significantly from the mean values for group 1. The elevated basal metabolic rates (mean, plus 19.0 per cent) probably represent poor tests, due to inability of the patient to relax during the test period.

4. Low basal metabolic rate without myxedema.—This group includes 11 patients, 1 man and 10 women, whose average age was 43.0 years. Like the previous group these patients had no evident organic disease and their symptoms were of a functional character. In addition, they were found to have abnormally reduced basal metabolic rates, but lacked objective clinical evidence of myxedema or pituitary disease on physical examination. Serum cholesterol values and protein-bound iodine values, when obtained, were within normal limits. In 4 patients treated with desiccated thyroid, the response in clinical symptoms and in the basal metabolic rate was that characteristic of euthyroid persons, not that of myxedematous patients. All five urinary radioiodine values were normal. Mean TA and AR were slightly but not significantly reduced. The lowered basal metabolic rates (mean, minus 22.5 per cent) in this group are considered to be due to nonthyroidal factors.

5. Essential hypertension.—This category comprises 15 patients (7 men, 8 women, average age 51.9 years) with varying degrees of essential hypertension but without evident impairment of cardiac or renal function. Such patients, particularly those more severely affected, often have elevated basal metabolic rates (presumably nonthyroidal). The mean basal metabolic rate was plus 17.8 per cent. Since hypertensive patients frequently exhibit a stimulated appearance suggestive of hyperthyroidism and sometimes have an incidental nodular goiter, the question of hyperthyroidism sometimes becomes extraordinarily difficult to answer. The patients included in this category, however, had normal thyroid glands on palpation, and aside from the stimulated appearance had no stigmata of hyperthyroidism. None of the radioiodine values was significantly different from those of the preceding groups.

6. Heart disease without decompensation.—The 8 patients comprising this group (5 men and 3 women, average age 44.0 years) all had severe heart disease without cardiac decompensation, impaired renal function or evidence of thyroid disease. One of the patients had coarctation of the aorta. Three had severe coronary sclerosis, 3 had rheumatic endocarditis with mitral stenosis, and 1 had calcareous aortic stenosis. All had had clinical symptoms of limited cardiac reserve. Elevation of the basal metabolic rate is often encountered in such cases. In part, this may be related to dyspnea or orthopnea, in part to apprehension; but there remains a question as to whether some hypermetabolism actually occurs in heart disease which cannot be explained on such a basis. As in the case of hypertension, the question of hyperthyroidism may be extremely difficult to settle in such patients, particularly if incidental goiter is present. At the same time, the

control of hyperthyroidism, if it exists, is of especial importance because of the coexisting heart disease.

The mean basal metabolic rate in this group was plus 2.8 per cent. Of the radioiodine values only those for DR and RER (means, 8.6 and 5.4 per cent per hour) are significantly lower ($p = 0.05$) than normal. The possibility exists that in this group of cases are some in which impaired renal function was unrecognized.

7. Heart disease with cardiac decompensation.—This group comprises 14 patients, 7 men and 7 women; their average age was 56.2 years. Four patients had rheumatic heart disease, 3 had arteriosclerotic heart disease and 7 had hypertensive heart disease. The mean basal metabolic rate was elevated as in the preceding group. The mean UE, RF and DR were all significantly less than in the previous normal groups. This circumstance could be interpreted as indicating that these patients had some increase of the iodine-accumulating function of the thyroid or else that the presence of edema fluid might in some manner have modified the behavior of radioiodine. The reduction of mean ERDR suggests that thyroidal function may be reduced, a view supported by a mean AR of 1.4 per cent per hour, which is significantly lower than the values for the preceding groups. The mean RER of 2.8 per cent per hour, shows clearly that the erroneous impression of increased thyroid collection provided in some cases by the other values is the result, not of increased thyroid function, but of diminished renal function with respect to iodine. Thirteen of the 14 patients had conspicuous albuminuria and 6 of them had significantly elevated blood urea.

8. Renal insufficiency.—The 5 patients included in this category (4 men and 1 woman, average age 47.4 years) all had clinically evident renal insufficiency at the time of study. The blood urea ranged from 54 to 198 mg. per 100 cc. at the time observed. One patient had multiple myeloma, 2 had intercapillary glomerulosclerosis, 1 had nephrosclerosis and 1 had chronic glomerulonephritis with an associated nephrotic syndrome. Three of the 5 patients were dead when this paper was written, 2 having died within four weeks of study and 1 within six months. Elevated metabolic rates occurred in 3 of the 5 cases. The same circumstances related in the preceding group are observed in this group also and probably for similar reasons; UE, RF and DR all tended to be low. This is principally due to impaired renal excretion of radioiodide as evidenced by a mean RER of 1.2 per cent per hour. Curiously enough, ERDR is likewise low. Similar values for RER and ERDR have been observed by Mason and Oliver (11) in 4 cases of Bright's disease with nitrogen retention. Instead of being increased, as the values for UE and RF might suggest, the iodine-accumulating function is thus found to be impaired in these cases. This is confirmed in the only one of the 5 cases in which AR could be calculated from in vivo observations. This value was 1.3 per cent per hour, which is quite low; the twenty-four-hour accumulation of iodine in the thyroid in this particular case was 26.0 per cent of the dose, a normal value.

9. Addison's disease.—This group includes 10 patients (4 men and 6 women, average age 40.9 years) who had classic untreated Addison's disease and no evident abnormality of the thyroid gland. The basal metabolic rate was a little low in the group as a whole, a finding characteristic of this condition. Of the values obtained from urinary studies only the disappearance rate and renal excretion rate are significantly reduced from the values in other groups. In some but not all of the cases, the thyroidal function as indicated by ERDR or by in vivo observations appeared to be reduced. In the only one of the 10 cases available for in vivo observation, the twenty-four-hour collection of radioiodine was 3.6 per cent of the dose, a low value, and AR was 0.7 per cent per hour. ERDR in this case was 2.7 per cent per hour, which adequately reflects this reduced accumulation rate.

B. Euthyroid conditions associated with thyroid disease

10. Malignant thyroid tumors.—This category includes 75 patients (27 men and 48 woman, average age 46.7 years) with various malignant lesions of the thyroid. In 42 cases the diagnosis was grade 1 papillary or nonpapillary adenocarcinoma, in 9 cases grade 2, in 7 cases grade 3, and in 8 cases grade 4. In 9 cases the grade of malignancy was not recorded. All but 10 patients were in good physical condition despite their disease at the time of study. In no case was there clinical or laboratory evidence of altered thyroid function.

The basal metabolic rate for this group of patients (mean, minus 0.7 per cent) and the range of distribution (standard deviation 9.2 per cent) were the same as for the normal. The mean values for urinary observations and in vivo observations as well as the distribution of these values were the same as for the normal groups. In 12 cases the neoplasm was demonstrated to be functioning on the basis of collecting significant amounts of radioiodine. This classification was based on uptake of I^{131} by cancer tissue exceeding 0.1 per cent per gram measured on surgically excised specimens. No significant differences appeared when these cases were compared with 25 cases in which surgical tissue showed less than 0.1 per cent per gram. Patients were compared on the basis of general physical condition. The group of 10 who were ill showed some equivocal changes similar in direction to those in groups 7, 8 and 9. Comparison on the basis of the grade of malignancy, on the basis of the presence or absence of roentgenologic evidence of metastasis, and on the basis of previous therapy, including previous surgical, roentgen and radium treatment, all failed to show significant differences within this group.

11. Adenomatous goiter without hyperthyroidism.—This category comprises 49 patients who had typical enlargement of the thyroid with nodules, either single or multiple, but in whom the presence of hyperthyroidism could be unequivocally excluded. The series includes 13 men and 36 women and the average age was 48.6 years. Subtotal thyroidectomy was performed in 37 of the cases. Pathologic examination of the tissue excised showed fetal and colloid adenomas in a colloid thyroid without evidence of parenchymatous hypertrophy of extra-adenomatous tissue (that is, exophthalmic goiter) on the one hand, or neoplasm or thyroiditis on the other. Five patients had elevated basal metabolic rates considered to be associated with accompanying hypertension. In these an additional criterion of euthyroidism was failure of the basal metabolic rate to change significantly after subtotal thyroidectomy.

The mean value for ERDR is slightly increased but the increase is of questionable significance (p value $=0.05$). The means for the other radioiodine values do not differ significantly from the normals. It may be significant, however, that the range of values in this group is much greater in the case of all these values than for the groups previously discussed. No matter how measured, the radioiodine-accumulating function varies much more from the mean in patients having adenomatous goiter than in the preceding ones discussed. This observation is of considerable diagnostic importance and will be discussed later.

In 15 of the cases there was a solitary adenoma in an otherwise normal thyroid gland and in 34 cases there were several and usually many nodules. No differences were observed in mean values or distribution when these groups were compared with one another, despite the fact that some students consider solitary thyroid adenomas and multiple nodular goiter to be distinct entities having different etiologies.

No significant correlation was observed between radioiodine accumulation and estimated thyroid weight (correlation coefficient $+0.19$; p value >0.05). Radioiodine accumulation was found to be inversely correlated with basal metabolic rate (correlation coefficient -0.35; p value <0.05). Although this is not a high degree of correlation, it is

nevertheless probably a significant one. It is possible that it may be related to the intrinsic iodine want characteristic of endemic goiter and may suggest a partial explanation for the variability of radioiodine accumulation in goitrous patients.

12. Colloid goiter.—That this condition is now rare is evidenced by the fact that only 3 patients could be found for study. All were women; their average age was 23 years. The goiters were moderately enlarged (estimated weight 50 Gm.) and soft, and no nodules could be felt. There was no clinical evidence on history, physical examination or laboratory findings of altered thyroid function, and the patients were all in good health. The radioiodine values are consistent with moderate increase in accumulating function of the thyroid. In the 2 cases in which in vivo data were obtained, the results are consistent with the same interpretation.

13. Exophthalmos of Graves's disease.—The group includes 23 patients (9 men and 14 women, average age 38.0 years) without goiter and without clinical evidence of hyperthyroidism who had ophthalmopathy of a type considered characteristic of Graves's disease. In 12 cases there was asymmetric ("unilateral") proptosis. In 11 cases the disturbance obviously affected both eyes. Careful ophthalmologic examination was considered to have excluded other causes for the condition in each instance. In 3 cases there was a record or history suggesting or confirming previous exophthalmic goiter, and in 2 of these thyroidectomy had been performed previously. In these cases the inference that the patients actually were suffering from the ophthalmologic features of Graves's disease without goiter and without hyperthyroidism can readily be defended. In the remaining cases, no data obtained would contradict the assumption that the condition was "idiopathic" or "agnogenic," completely unrelated to Graves's disease beyond the fact that the ophthalmologic findings, and particularly the appearance of the eyes, resembled in all respects those commonly encountered in the classic form of exophthalmic goiter.

All of the mean radioiodine values as well as the basal metabolic rates were essentially identical with those of the normal group. The values varied somewhat more than did the normal, as evidenced by larger standard deviations for forty-eight-hour urine, renal fraction, disappearance rate and extrarenal disposal rate. When the data obtained in cases with prior history of exophthalmic goiter or of thyroidectomy were compared with data from those without this history, the results were not significantly different. No differences were disclosed by comparison of cases with apparent "unilateral" involvement and those in which both eyes were obviously affected.

C. Hyperthyroid conditions

14. Exophthalmic goiter.—A group of 143 cases of exophthalmic goiter were studied, in 20 of which there was associated heart disease with decompensation. These 20 cases will be considered separately (group 15). In the present group of 123 patients there were 39 men and 84 women, with an average age of 38.0 years. The diagnosis was established on the basis of 1) history, clinical signs and symptoms, including ophthalmologic signs if present; 2) a classic response to the preoperative administration of iodides with regard to the clinical symptoms, to the consistency of the thyroid gland and to the level of the basal metabolic rate; 3) the finding of diffuse parenchymatous hypertrophy on examination of the surgical specimen (47 cases); and 4) a satisfactory remission of the disease after operation or after treatment with I^{131} or antithyroid drugs (all cases). Obviously, not all of the criteria were met in all cases and judgment was exercised in deciding about the diagnosis in those instances in which it was not possible to evaluate all the criteria listed. In all the cases, however, the evidence, appraised entirely independently of the results of radioiodine studies, warranted an unequivocal diagnosis of exophthalmic goiter.

The mean basal metabolic rate for 123 cases was plus 34.2 per cent. The mean radioiodine values unequivocally indicated higher iodine-accumulating function of the thyroid than normal by a wider margin than encountered in any previous group. Thus the mean value for UE was 25.4 per cent of the dose, and for RF 24.3 per cent of the dose, both values being less than half those of the euthyroid groups. DR was 30.9 per cent per hour, nearly three times the normal value; ERDR was 25.0 per cent per hour, more than six times the normal value; TA was 63.2 per cent of dose, more than twice the normal value; and AR was 22.1 per cent per hour, more than seven times the normal value. Only RER, 5.9 ± 0.2 per cent per hour, was not markedly altered. This value, which measures renal, not thyroidal function, is somewhat lower than in the normal group but this is of doubtful significance (p value $= 0.05$).

In 11 cases there were one or more nodules in the thyroid in addition to the diffuse parenchymatous hypertrophy characteristic of exophthalmic goiter. Cases with such incidental "cold" nodules are generally classified as exophthalmic goiter with adenomas, or as exophthalmic goiter occurring in pre-existing adenomatous goiter. Comparison of the data showed no statistically significant difference between those cases of exophthalmic goiter which had incidental nodules and those which did not.

In 57 cases the disease was recurrent, with a history of one or more episodes of exophthalmic goiter a year or longer preceding the episode being studied; in 54 of these, thyroidectomy had been performed previously. Comparison of the data in this group with those obtained in 66 cases of primary exophthalmic goiter likewise failed to show significant differences.

A slight but significant correlation was found between the size of the thyroid and radioiodine accumulation data: ERDR (correlation coefficient $+0.28$, $p < 0.01$). However, some cases with very small thyroids displayed very pronounced avidity for iodine, whereas some very large thyroids differed little from the normal in this regard.

Of considerable practical and theoretic interest is the question whether radioiodine accumulation could be correlated with the severity of thyrotoxicosis or with the basal metabolic rate, which is to some degree an acknowledged index of severity. A moderate but significant correlation was found (correlation coefficient $+0.33$, $p < 0.01$).

In general the severest cases with the highest basal metabolic rates also had marked alteration in radioiodine accumulation. Some cases, however, which clinically were very severe and in which the metabolic rates were very high showed only moderate alteration of radioiodine accumulation. Others that were clinically mild and difficult to diagnose, with basal metabolic rates close to the normal range, had a surprisingly marked increase in radioiodine-accumulating function. This observation has the obvious implication that evaluation of the radioiodine tracer may be a useful adjunct to the basal metabolic rate in difficult diagnostic problems, since it may be unequivocally altered when the basal metabolic rate is normal or at most slightly elevated. If a very high correlation between radioiodine collection and basal metabolism has been found, the usefulness of radioiodine tracers would have to be considered more in the light of their relative value as alternatives rather than as adjuncts to the basal metabolic rate. Furthermore, the limited extent to which correlation is found lends further support to the concept that basal metabolic rate and radioiodine tracer studies measure aspects of thyroid function which may be more or less independent and which do not necessarily vary in proportion to one another.

Data on the patients having exophthalmic goiter were analyzed to determine if any correlation existed between the degree of exophthalmos observed and the accumulation of radioiodine. Only those cases were used in which the records were reasonably clear with regard to the extent of the exophthalmos. They were divided into three groups:

those without clinically significant exophthalmos, those with minimal exophthalmos and those with severe exophthalmos. The results are summarized in Table 3, which includes for comparison the cases listed as exophthalmos of Graves's disease without hyperthyroidism and without goiter (group 13). The last group is obviously distinct from the preceding ones in that the patients have no elevation of basal metabolic rates and show euthyroid radioiodine accumulation. No significant differences exist between the remaining three groups. The observations made in the last group agree with those of Hertz and Roberts (20), Skanse (5), and Werner, Quimby and Schmidt (19) in cases of hyperophthalmopathic Graves's disease, but there is very little evidence of intergradation between this condition and cases of typical exophthalmic goiter.

15. Exophthalmic goiter associated with cardiac decompensation.—Because of the finding (group 7) that cardiac decompensation resulted in reduction of the rate of disposal of

TABLE 3. COMPARISON OF RADIOIODINE ACCUMULATION WITH VARYING DEGREES OF EXOPHTHALMOS

Group	No. of cases	Basal metabolic rate, per cent	Extrarenal disposal rate, per cent per hour
Exophthalmic goiter without clinically significant exophthalmos	62	+37.0±1.8*	24.6±1.9
Exophthalmic goiter with minimal exophthalmos	20	+35.8±4.0	23.3±3.4
Exophthalmic goiter with severe exophthalmos	7	+32.4±3.7	20.0±3.0
Exophthalmos of Graves's disease without hyperthyroidism and without goiter	23	−4.5±2.1	4.5±0.5

* The values given are the means and standard errors of the mean.

radioiodine by both thyroid and kidneys, 20 cases of exophthalmic goiter having this complication were analyzed separately. The group comprised 6 men and 14 women, and the average age was 55.8 years. The criteria for the diagnosis were the same as for the preceding category. Five of the patients had accompanying hypertensive heart disease, 4 patients had coronary heart disease, 5 had rheumatic heart disease, 1 had constrictive pericarditis and in 5 cases the cardiac failure was attributed to hyperthyroidism per se.

The mean RER (4.2 per cent per hour) was significantly less than in the previous group and other groups with normal renal function. The other radioiodine values obtained were not significantly different from those for exophthalmic goiter without decompensation.

16. Adenomatous goiter with hyperthyroidism.—We believe, as did Plummer (21), that this condition is an entity which is physiologically distinct from exophthalmic goiter and which commonly develops as an incident in the life history of endemic goiter. Patients were so classified who had nodular enlargement of the thyroid with unequivocal evidence of hyperthyroidism, but absence of the ocular signs and neuromuscular excitability characteristic of exophthalmic goiter. The patients showed at best an equivocal response to

the exhibition of iodides and usually no response to it. Pathologic examination of the excised thyroid showed single or multiple fetal or colloid adenomas but no evidence whatever of parenchymatous hypertrophy of extra-adenomatous tissue. Removal of the goiter was followed by clinical improvement of the signs and symptoms of hyperthyroidism and a significant reduction of the basal metabolic rate, usually to normal values. In all of the cases in this category all of the foregoing criteria were met.

There were 25 patients, of whom 4 were men and 21 were women. The average age was 57.4 years. The mean basal metabolic rate was plus 29.7 per cent, a little less than the mean for exophthalmic goiter. The radioiodine accumulation by the thyroid was increased in this group on the average, but the changes from the normal differed from those encountered in the preceding two groups in two respects; 1) the mean values were not altered nearly so much as in exophthalmic goiter; 2) many of the values fell within the normal range.

In 5 cases there was a solitary hyperfunctioning adenoma. In the remainder, two or more nodules were present. No significant differences were disclosed on comparison of the data of these two groups.

No correlation could be found between radioiodine accumulation and basal metabolic rate (correlation coefficient $+0.14$; p value >0.05) or between radioiodine accumulation and size of the thyroid (correlation coefficient $+0.08$; p value >0.05). This may be due to the small number of observations in this group; such correlations might conceivably be encountered in larger series.

17. Acromegaly.—Seven patients (2 men and 5 women, average age 46.4 years) were studied who were considered to have clinically active acromegaly. Enlargement of the thyroid was observed in 6. The mean basal metabolic rate was plus 20.1 per cent and the values varied from plus 9 to plus 39 per cent. Radioiodine values were essentially normal. In 2 cases in which in vivo data were obtained, these were also entirely normal.

D. Hypothyroid states

18. Myxedema.—In this category were placed all cases with unequivocal clinical criteria of spontaneous or postoperative myxedema which was untreated at the time of the study. All had unequivocal signs and symptoms of the disease, depressed basal metabolic rate and serum protein-bound iodine (when determined), and elevated serum cholesterol. The laboratory criteria and clinical findings responded characteristically to the exhibition of desiccated thyroid in suitable amounts. The group included 46 patients, of whom 9 were men and 37 were women, with an average age of 48.8 years.

The average basal metabolic rate was minus 25.9 per cent. The average UE was 76.7 per cent of the dose. In hypothyroid states, as noted by Skanse (5), forty-eight hours is an inadequate period of time for evaluation of the complete urinary excretion. This is indicated by the disparity between the foregoing value and mean RF for this group, which was 81.7 per cent of the dose. Mean DR (6.6 per cent per hour) is significantly less than in euthyroid groups. Mean RER (5.4 per cent per hour) is also significantly reduced. Mean ERDR (1.2 per cent per hour) is only 30 per cent of the normal value. In vivo observations in 28 of the 46 cases showed an average accumulation after twenty-four hours of 4.8 per cent of the dose, and mean AR of 0.3 per cent per hour. Seventeen of the cases showed no collection whatever, and had 0 accumulation rate. In the remaining 11 cases for which such data were available, the TA varied from 1.5 to 16.6 per cent after twenty-four hours, and AR varied from 0.1 to 1.3 per cent per hour.

In 8 cases the myxedema had occurred after subtotal thyroidectomy for exophthalmic goiter. In the remaining 38 cases the condition was spontaneous with neither history

those without clinically significant exophthalmos, those with minimal exophthalmos and those with severe exophthalmos. The results are summarized in Table 3, which includes for comparison the cases listed as exophthalmos of Graves's disease without hyperthyroidism and without goiter (group 13). The last group is obviously distinct from the preceding ones in that the patients have no elevation of basal metabolic rates and show euthyroid radioiodine accumulation. No significant differences exist between the remaining three groups. The observations made in the last group agree with those of Hertz and Roberts (20), Skanse (5), and Werner, Quimby and Schmidt (19) in cases of hyperophthalmopathic Graves's disease, but there is very little evidence of intergradation between this condition and cases of typical exophthalmic goiter.

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In 5 cases there was a solitary hyperfunctioning adenoma. In the remainder, two or more nodules were present. No significant differences were disclosed on comparison of the data of these two groups.

No correlation could be found between radioiodine accumulation and basal metabolic rate (correlation coefficient $+0.14$; p value >0.05) or between radioiodine accumulation and size of the thyroid (correlation coefficient $+0.08$; p value >0.05). This may be due to the small number of observations in this group; such correlations might conceivably be encountered in larger series.

17. Acromegaly.—Seven patients (2 men and 5 women, average age 46.4 years) were studied who were considered to have clinically active acromegaly. Enlargement of the thyroid was observed in 6. The mean basal metabolic rate was plus 20.1 per cent and the values varied from plus 9 to plus 39 per cent. Radioiodine values were essentially normal. In 2 cases in which in vivo data were obtained, these were also entirely normal.

D. Hypothyroid states

18. Myxedema.—In this category were placed all cases with unequivocal clinical criteria of spontaneous or postoperative myxedema which was untreated at the time of the study. All had unequivocal signs and symptoms of the disease, depressed basal metabolic rate and serum protein-bound iodine (when determined), and elevated serum cholesterol. The laboratory criteria and clinical findings responded characteristically to the exhibition of desiccated thyroid in suitable amounts. The group included 46 patients, of whom 9 were men and 37 were women, with an average age of 48.8 years.

The average basal metabolic rate was minus 25.9 per cent. The average UE was 76.7 per cent of the dose. In hypothyroid states, as noted by Skanse (5), forty-eight hours is an inadequate period of time for evaluation of the complete urinary excretion. This is indicated by the disparity between the foregoing value and mean RF for this group, which was 81.7 per cent of the dose. Mean DR (6.6 per cent per hour) is significantly less than in euthyroid groups. Mean RER (5.4 per cent per hour) is also significantly reduced. Mean ERDR (1.2 per cent per hour) is only 30 per cent of the normal value. In vivo observations in 28 of the 46 cases showed an average accumulation after twenty-four hours of 4.8 per cent of the dose, and mean AR of 0.3 per cent per hour. Seventeen of the cases showed no collection whatever, and had 0 accumulation rate. In the remaining 11 cases for which such data were available, the TA varied from 1.5 to 16.6 per cent after twenty-four hours, and AR varied from 0.1 to 1.3 per cent per hour.

In 8 cases the myxedema had occurred after subtotal thyroidectomy for exophthalmic goiter. In the remaining 38 cases the condition was spontaneous with neither history

nor physical findings to indicate local thyroidal disease. Comparison of observations in these two groups disclosed no significant differences between them.

19. Anterior pituitary insufficiency.—Four women and 1 man having severe untreated pituitary insufficiency were observed. These included 3 patients who had Sheehan's syndrome (postpartum pituitary necrosis) and 2 patients who had chromophobe adenoma, 1 of whom (the man) had pituitary dwarfism. The average basal metabolic rate for the the group was minus 26.4 per cent. The mean radioiodine values were essentially the same as for the group having primary thyroprivic myxedema.

Three of the patients had clinically evident myxedema in addition to the features of pituitary insufficiency. They displayed characteristic dryness of the skin, slowed tendon reflexes, slowed speech, and hypercholesteremia. The remaining 2 patients had clear-cut pituitary insufficiency, but lacked the specific evidences of myxedema enumerated. All patients showed low values for radioiodine accumulation.

20. Acute diffuse thyroiditis.—This condition is defined as a subacute or acute illness characterized by fever, malaise, an enlarged, firm, exquisitely tender thyroid gland and a very high sedimentation rate. The group comprises 16 patients, of whom 3 were men and 13 were women. The average age was 43.8 years. Transitory hyperthyroidism was present during the time of study in 1 case. The remainder were clinically euthyroid. In at least 4 patients, myxedema developed some months later. In 5 other patients who were followed for several months myxedema did not develop. For 7 patients no follow-up is available.

The basal metabolic rates were within the normal range; the mean value (plus 5 per cent) is significantly greater than for the euthyroid groups. Surprisingly, all of the radioiodine data are unequivocally and consistently in the range characteristic of myxedema, and do not differ significantly from the values observed in the preceding group. In vivo observations were available in 10 cases. Mean TA was 4.9 per cent of dose; mean AR was 0.5 per cent per hour. In 5 of these cases, no thyroidal collection whatever was detected. In only 1 of the remainder did the values approach normal, 13.1 per cent after twenty-four hours. Protein-bound iodine was measured in 4 of these cases and the values obtained were 4.4, 8.8, 9.3 and 9.6 micrograms per 100 cc. respectively.

Abnormally low values for twenty-four-hour thyroidal accumulation were found by Werner and associates (19) in all 6 of the patients that they observed with this condition.

21. Hashimoto's thyroiditis (struma lymphomatosa).—The 7 patients comprising this group were all demonstrated to have generalized struma lymphomatosa at subsequent operation. One patient was a man and 6 were women; the average age was 42.8 years. Five of the 7 patients had frank myxedema at the time of the study; the remaining 2 did not. The average basal metabolic rate for the group was minus 17.3 per cent. All the values for radioiodine accumulation were unequivocally normal. This was also true of the 5 cases having frank clinical myxedema. The results of in vivo studies of 4 of the patients having frank myxedema were likewise normal.

22. Riedel's thyroiditis (struma ligneosa).—The 4 patients included under this heading were all demonstrated to have diffuse struma ligneosa at subsequent operation. None of the patients had myxedema at the time of study. Two patients were men and 2 were women, the average age being 51.5 years. The radioiodine values obtained indicated iodine-accumulating function somewhat higher than in the myxedematous group but far lower than normal.

23. Thiocyanate myxedema.—Fifteen patients were encountered in whom evidence of myxedema had developed after treatment of essential hypertension with potassium

thiocyanate. Eleven of the patients had enlargement of the thyroid and 4 did not. Four patients were men and 11 were women; the average age was 51.2 years.

The symptoms of myxedema were fairly typical in most respects, but in several instances the basal metabolic rate was not abnormal. Whether this was due to the underlying hypertension or some other factor could not be ascertained. In all instances, the evidences of myxedema receded gradually within weeks or months after administration of the drug had been discontinued and without replacement therapy. The enlargement of the thyroid likewise receded excepting in 1 patient known to have had a pre-existing adenomatous goiter. The mean values for radioiodine tracer studies were suggestive of slightly higher uptake than in other myxedematous groups. A good deal of variation occurred from case to case. One patient, having a considerable enlargement of the thyroid and blood thiocyanates of 6.0 mg. per 100 cc., had a high accumulation of radioiodine (extrarenal disposal rate 13.3 per cent per hour; twenty-four-hour accumulation 60 per cent of dose; accumulation rate 10.3 per cent per hour). Another patient with a thyroid gland essentially normal to palpation and blood thiocyanates of 6.0 mg. per 100 cc. had essentially normal values. The remaining 13 patients had blood thiocyanate values between 5.0 and 11.9 mg. per 100 cc. and reduced accumulation values.

Many of these patients were followed intensively. The wide variation in accumulating function with varying size of thyroid enlargement and levels of thiocyanate in the blood will be discussed in another publication.

E. Miscellaneous conditions

Random observations were obtained in 17 patients with conditions not discussed in the preceding sections. These are enumerated in Table 4.

Anorexia nervosa.—Tracer studies were made of 3 women who had anorexia nervosa. Radioiodine accumulation was normal or perhaps even a little high in these cases. Werner, Quimby and Schmidt (19) observed normal twenty-four-hour accumulation in 6 cases. The difference between these observations and those in pituitary insufficiency may prove diagnostically useful.

Exogenous hyperthyroidism.—This condition was suspected in 3 cases but confirmed in none of them. All were clinically hyperthyroid, all had elevated basal metabolic rates and all had myxedema-like results of tracer tests. In the absence of positive proof that the patients were taking thyroid in excessive quantities, these cases actually belong in the "equivocal" category. Previous reports (22) have emphasized the usefulness of radioiodine tracer studies in diagnosing this condition. It should be emphasized, however, that patients with bona fide exophthalmic goiter have been encountered who unaccountably had no measurable radioiodine accumulation. Similar reactions in exophthalmic goiter will be described resulting from ingestion of iodides, Priodax, cyanates and antithyroid drugs. Therefore, absence of iodine accumulation in thyrotoxic persons cannot be taken as absolute proof of exogenous hyperthyroidism.

Chronic alcoholism.—This condition may simulate acute hyperthyroidism very closely; the patients lose weight, appear intensely stimulated, develop a marked fine tremor, perspire excessively and have tachycardia. In addition the basal metabolic rate is high. If the patient successfully conceals his breath and the extent of his drinking, an erroneous diagnosis of exophthalmic goiter is sometimes made. In the 3 cases of this type studied, the results of radioiodine tests were unequivocally normal.

Nontropical sprue.—One patient was studied in whom this diagnosis had been established with reasonable certainty. The patient had an elevated basal metabolic rate, a

condition occasionally noted in such patients, but no other evidences of hyperthyroidism. Radioiodine values were normal.

Hyperplastic thyroid nodules.—One euthyroid patient was observed who previously had undergone subtotal thyroidectomy elsewhere for exophthalmic goiter and who sought advice only because of a prominent nodule which had gradually appeared in the midline below the laryngeal cartilage. The results of radioiodine studies were de-

TABLE 4. MISCELLANEOUS CASES

Case	Diagnosis	Basal metabolic rate, per cent	48-Hour urinary excretion, per cent of dose	Renal excretion rate, per cent per hour	Extrarenal disposal rate, per cent per hour	24-Hour thyroidal accumulation, per cent of dose	Accumulation rate, per cent per hour
1	Anorexia nervosa	−13	64.4	10.0	5.4		
2	Anorexia nervosa	−40	46.0	4.7	6.5		
3	Anorexia nervosa	−22	56.0	7.0	7.5	40.0	7.8
4	Exogenous hyperthyroidism (?)	+68	92.0	13.4	1.5		
5	Exogenous hyperthyroidism (?)	+45	72.7	5.7	1.8	0	0
6	Exogenous hyperthyroidism (?)	+38	88.8	6.2	1.6		
7	Chronic alcoholism	+13	54.2	8.0	7.0		
8	Chronic alcoholism	+18	61.9	6.3	3.7	29.9	3.3
9	Chronic alcoholism	+27	53.8	5.8	6.3	30.1	3.8
10	Sprue	+32	55.6	10.5	9.0	41.0	7.8
11	Hyperplastic thyroid nodule suspected	− 3	25.8	4.2	12.9	56.0	10.0
12	Exophthalmic goiter in lupus erythematosus	+38	27.7	2.5	7.6	75.9	7.0
13	Addison's disease and myxedema	−24	47.9	4.5	4.8	35.8	3.8
14	Addison's disease and myxedema	−18	64.3	2.6	0.7	7.2	0.4
15	Ovarian agenesia with dwarfism	+30	65.7	9.8	4.9		
16	Cushing's syndrome	−22	63.1	5.6	2.4		
17	Primary muscular atrophy	+15	45.8	5.1	5.9		

cidedly hyperthyroid in character. In vivo studies showed that the nodule contained all of the radioiodine in the neck. At the patient's insistence it was excised and found to consists of hyperplastic thyroid tissue weighing 4 grams. Myxedema promptly developed.

Exophthalmic goiter complicating disseminated lupus erythematosus.—The patient studied with this combination of conditions, was of interest particularly because of rather severe renal insufficiency. The blood urea was 69 mg. per 100 cc. and RER was 2.5 per cent per hour. The diagnosis of exophthalmic goiter was clinically clear-cut. The case is of

interest because, although the quantities of radioiodine were typical of exophthalmic goiter, the radioiodine rates were not.

Addison's disease with myxedema.—Two cases were studied in which the coexistence of these conditions was established with reasonable certainty. Both showed somewhat reduced renal excretion. One case had normal radioiodine accumulation; in the second it was reduced. The latter is an excellent illustration of an instance in which the quantity excreted in the urine in forty-eight hours can be erroneously interpreted to indicate normal function.

One patient with ovarian agenesia with dwarfism, 1 with active Cushing's syndrome and 1 with primary muscular atrophy were also observed. All had radioiodine values which were quite normal. Unfortunately no observations were obtained in patients with blood dyscrasias including leukemia.

F. The effects of iodides and of iodine-containing compounds on diagnostic radioiodine studies

Six hundred and seventy-seven cases in which the diagnosis was certain and the data were adequate were reviewed with reference to the administration of iodine or of iodine-containing substances. The results were as follows:

TABLE 5. EFFECT OF IODIDES (STRONG SOLUTION OF IODINE [LUGOL'S SOLUTION]) ON RADIOIODINE ACCUMULATION IN CASES OF EXOPHTHALMIC GOITER

Time after omission of iodides	No. of cases	Basal metabolic rate, per cent	Renal excretion rate, per cent per hour	Extrarenal disposal rate, per cent per hour
During	7	+29.9±6.6*	6.7±0.8	1.8±0.6
1–2 days	9	+43.0±3.4	5.3±0.7	8.3±2.9
3–6 days	8	+30.3±8.0	4.8±0.7	13.2±3.8
7–10 days	12	+32.5±4.3	5.9±0.8	24.6±3.4
11–20 days	10	+31.0±4.3	6.6±1.0	25.7±3.6
21–30 days	6	+24.8±3.9	6.4±0.8	26.0±6.9
1–6 months	10	+29.0±3.0	6.0±0.4	24.6±5.0

* The values given are the means and standard errors of the mean.

Inorganic iodides in exophthalmic goiter.—There were 62 cases of exophthalmic goiter in the series in which the patient was taking iodides or had been taking iodides in therapeutic quantities within six months. The results observed in these cases, grouped according to the interval which had elapsed since iodides were last taken, are summarized in Table 5. The mean values and standard errors of the means for extrarenal disposal rate are given, and for comparison the basal metabolic rate and the renal excretion rate, a value unrelated to thyroidal function, are also included. Other measures of iodine accumulation (UE, TA and AR) all disclosed changes similar to those shown.

The mean value for extrarenal disposal rate for patients receiving iodide at the time of the radioiodine study, 1.8 per cent per hour, is comparable to that encountered in myxedema. In vivo studies showed negligible accumulation. Values rose rapidly on withdrawal of iodides and the mean values for patients who had not received iodides for seven days or longer were substantially identical to those in the larger series (Table 2, group

14). On the basis of this study, all patients who had had iodides within three weeks were excluded from the diagnostic study (Table 2).

In 5 cases of exophthalmic goiter studied while iodides were being administered, tracer studies were repeated at four-day intervals after treatment was omitted. The results observed in these individual instances were similar to those previously given: within five to nine days after withdrawal of iodides the radioiodine accumulation increased to thyrotoxic levels. Repeated studies after longer intervals showed no further significant change in 4 cases. In the fifth case a sustained increase in radioiodine accumulation for two weeks paralleled a rising basal metabolic rate and increasing severity of symptoms of exophthalmic goiter.

The time interval involved ($7 \pm$ days) is of the same order as that required for the very high levels of plasma inorganic iodide present during iodide therapy (1,000 to 5,000 micrograms per 100 cc.) to fall to the low levels found in untreated exophthalmic goiter (less than 1.0 microgram per 100 cc.). This can be estimated for individual cases from the rate of disappearance of radioiodine from blood in thyrotoxic patients having high levels of plasma iodide, and has been confirmed by direct observation of plasma iodide (I^{127}) concentration after omission of iodide therapy. It would thus seem that the phenomenon observed represents either a relative or an absolute suppression of radioiodine accumulation (that is, hormonal biosynthesis) resulting from a large excess of plasma inorganic iodide; as soon as this has had time to disappear the excessive iodine accumulation characteristic of the hyperplastic thyroid reappears. The fact that the mean values after seven days or more without iodides are the same as those in untreated patients suggests that the intrinsic abnormal capacity to accumulate iodine was essentially unmodified by iodide therapy.

It is of interest that this appears to be true in our series irrespective of how long the patient had taken iodide, or whether a clinical "iodide effect" had occurred. Such a partial remission in the intensity of symptoms had occurred in many of the cases and in some instances this iodide effect had been sustained for weeks or months, according to the record. However, no reflection of such remission appears in the mean values for basal metabolic rate recorded in Table 5.

Skanse (5), in a similar appraisal of iodide effects on radioiodine accumulation, stated that the effect due to elevated plasma iodide lasts only two days but he furnished no evidence in support of this statement. He apparently feels that effects observed after a longer interval represent pharmacologic effects of the drug as distinguished from that due to elevated plasma iodide. The effect due to elevated plasma iodide is the only one which we feel can be detected in our data (Table 5) or in Skanse's (Table 26, page 88).

Werner, Quimby and Schmidt (19) observed very low radioiodine accumulation in 3 of 4 patients who had received iodides one and one-half to twelve weeks previously and concluded, we believe erroneously, that an inhibitory effect of iodides was therefore present for this period. Hertz and Roberts (20) had originally considered that an inhibitory effect of iodides on radioiodine accumulation might exist for six weeks or longer.

Iodides in euthyroid persons.—Twenty-one euthyroid patients were studied who had received iodide as strong solution of iodine (Lugol's solution), potassium iodide or cough mixtures during or within three weeks prior to study. The results were similar to those observed with exophthalmic goiter treated in this manner: radioiodine accumulation was nil during treatment and became normal about seven days after omission of the drug. All these cases were excluded from diagnostic study.

Excretory urography.—Eight hyperthyroid patients were studied one to twenty-six days after intravenous urography. The iodine-containing compound used for roentgeno-

graphic visualization was sodium iodomethamate (Neo-iopax). All of the values observed were in the normal or hyperthyroid range. Because of the small size of the series no conclusions could be drawn as to the effect of this compound. The fact that such substances are very rapidly excreted by the kidneys would suggest that the duration of any effect on thyroidal accumulation must be quite brief. Because this point could not be settled, however, these cases were not included in the diagnostic study.

Cholecystography.—Forty patients, of whom 15 were hyperthyroid, 19 euthyroid and 6 myxedematous, had radioiodine studies at intervals up to two years after administration of gallbladder dye, usually iodoalphionic acid (Priodax), for roentgenographic visualization of the gallbladder. The values indicating radioiodine accumulation were very low in most instances, even when the gallbladder dye had been given a year or longer prior to the study. Thus extrarenal disposal rate was less than 2 per cent per hour in 9 of 19 euthyroid patients and 6 of 15 hyperthyroid patients. Only 2 of 15 patients with hyperthyroidism had values which appeared elevated. In vivo observations in 1 case of exophthalmic goiter disclosed 51.1 per cent of the dose in the thyroid twenty-four hours after administration of the dose, despite ingestion of Priodax two weeks previously. The marked impairment of iodine accumulation which Priodax may produce evidently varies a great deal from case to case. Some patients, both euthyroid and hyperthyroid, were observed who showed very substantial radioiodine accumulation despite the ingestion of Priodax only a few weeks before; it is interesting that comparably great variation has been observed in the levels of protein-bound iodine in plasma after administration of gallbladder dyes. There may prove to be some correlation between the quantity of circulating plasma iodine from the dye and the degree of impairment of the radioiodine accumulation by the thyroid. Considering this variation, it is apparent that our series of cases is too small and too heterogenous a group to establish either the length of time that gallbladder dye alters the behavior of a tracer test or the basis for the widely variable results which are encountered. We have found it expedient to assume that radioiodine tracers may be altered by Priodax for a year or longer and accordingly have excluded all patients known to have received such material within two years from consideration in the diagnostic study. Since Priodax ordinarily inhibits radioiodine accumulation, the occasional instance in which, despite a previous roentgenogram of the gallbladder, a tracer test gives a result similar to that seen in hyperthyroidism it may safely be regarded as supporting that diagnosis.

Desiccated thyroid.—Skanse (5) has observed that in patients with exogenous thyrotoxicosis resulting from the ingestion of desiccated thyroid the urinary excretion of radioiodine may approach 100 per cent; in euthyroid patients receiving the drug, forty-eight-hour excretion varied considerably. We have observed the effects of thyroid medication in 9 patients considered not to have thyroid deficiency or myxedema on the basis of the history and clinical observations. The mean ERDR of these patients was 1.7 per cent per hour. In all but 1, the accumulation of radioiodine was nil by all criteria, although the period of omission of the drug varied from 0 to thirty days. In 1 case a normal collection was observed seven days after discontinuance of 2 grains (0.13 Gm.) of thyroid per day. It is not evident from our data how long the inhibitory effect of thyroid may persist.

G. The effect of antithyroid drugs on radioiodine accumulation

Propylthiouracil.—The work of Stanley and Astwood (23) has made it clear that propylthiouracil and allied compounds inhibit hormonal biosynthesis and hence radioiodine accumulation by the thyroid. However, they do not impair its ability temporarily

to trap inorganic iodide for a few hours. Rawson and his associates (24) observed that more than 55 per cent of a tracer dose was excreted by 10 out of 11 thyrotoxic patients receiving thiouracil. Skanse (5) obtained an average excretion of 49 per cent in forty-eight hours in 9 patients receiving propylthiouracil and 80 per cent in 1 patient receiving methylthiouracil. It is noteworthy that in none of these observations did the impairment of accumulating function observed approach that seen in patients receiving iodides. Our experience has been the same. Of 8 thyrotoxic patients studied while receiving propylthiouracil, only 1 had a normal extrarenal disposal rate; in the other 7 this was unequivocally elevated despite the therapy. In vivo measurements were also significantly elevated during therapy, although less so than after it had been discontinued. Under these circumstances it is difficult to estimate how long the effect of such antithyroid substances is continued. Of 16 cases studied after omission of propylthiouracil for three to sixty days, only 3 had values in the normal range. Our series of 24 cases is too small and the doses and conditions involved are too varied to permit any conclusions from our data regarding duration of effect. Skanse's data suggest that the impairment of radioiodine accumulation due to propylthiouracil is overcome completely in forty-eight hours or less. Nevertheless we have preferred to exclude from diagnostic study all patients who had received antithyroid drugs.

Results of animal studies suggest that if propylthiouracil or similar substances were given to a normal person long enough, hyperplasia of the thyroid and increased accumulation of radioiodine should result. Since patients who do not have exophthalmic goiter are occasionally given these drugs in the mistaken belief that they have the condition, and owing to poor response may be referred for diagnosis, the question is not an academic one. Of 5 euthyroid patients in our series who had received propylthiouracil only 1 had a definite increase in accumulation of radioiodine (ERDR 19.0 per cent per hour seven days after the drug had been omitted). It therefore seems reasonable to suppose that increase in accumulation of radioiodine may sometimes result in this manner, but we do not have enough data to predict the frequency with which it can be anticipated.

Thiocyanate.—Five patients were observed who had adenomatous goiter without hyperthyroidism and had received treatment with potassium thiocyanate for hypertension within one to fifty days of the tracer study. In 2 of these, radioiodine accumulation appeared to be normal; in the remaining 3 cases the values obtained were in the range characteristic of myxedema. No conclusion could be drawn regarding how often or how long this drug interfered with iodine accumulation. The very low excretion of thiocyanates by the kidneys and very slow disappearance from the blood would suggest that when inhibition of iodine accumulation has once been produced by this means it may take many weeks to disappear. The occurrence of compensatory hyperplasia of the thyroid, which might result from such therapy, could make evaluation of this effect very difficult (25).

COMMENT

From the foregoing it is evident that radioiodine tracer tests do, with some important exceptions, reflect alterations of thyroid function. Furthermore, excepting in conditions accompanied by altered renal function, or following ingestion of certain drugs, radioiodine-accumulating function by the thyroid appears comparatively unaltered in conditions not involving the thyroid. To employ the radioiodine tracer test as a diagnostic

aid in a given case, however, it is necessary to know how much the index of accumulating function to be used varies in normal persons and in patients having conditions not involving the thyroid. For practical purposes the diagnostic efficiency of the procedure can best be defined in two ways: 1) in terms of the number of patients with hyperthyroidism or hypothyroidism that fall within a normal or euthyroid range; that is, "false negatives"; and 2) in terms of the number of euthyroid patients whose values fall outside the normal or euthyroid range; that is, "false positives."

Range of values in euthyroid persons

The 11 cases classified as "normal" constitute too small a group, taken alone, to provide a statistically significant estimate of the range of variation to be expected in normal persons. It was not possible for us to obtain a statistically adequate series of normal observations because of concern about the quantity of radiation involved. The total integrated dose of radiation delivered to a normal thyroid gland receiving 100 microcuries of I^{131} may be of the order of 150 r.e.p. (roentgen equivalents physical) delivered at an initial rate of the order of 12 r.e.p. per day. We have not been willing to subject volunteers in large numbers to this dose of radiation. Skanse (5) obtained information regarding twenty-four-hour and forty-eight-hour urinary excretion of radioiodine in hospital personnel following a dose of 10 microcuries. This dose, which is probably not hazardous, has heretofore been inadequate with available technics for the detailed studies which we have wished to make, but entirely satisfactory for determination of total urinary excretion. Skanse found that the mean forty-eight-hour urinary excretion in 110 normal persons was 65.9 ± 0.07 per cent. Our value for 11 normal persons, 64.5 ± 1.4 per cent, is not significantly different from this. In fact, the close agreement between the two values is surprising in view of the fact that they were obtained in different geographic areas and by different technics. Range of distribution in our normal group ($\sigma = 4.8$) is considerably less than in Skanse's series ($\sigma = 7.8$) which only strengthens the suspicion that the smaller group cannot be regarded as safely delineating the normal range.

Skanse expressed the normal range in terms[1] of $\overline{M} \pm 2\sigma$, to $\overline{M} \pm 3\sigma$. Providing the observations follow a normal distribution (which is only approximately true in the case of forty-eight-hour urinary excretion), these estimated ranges should include 95 per cent to 99.7 per cent of the observations, respectively. Actually, however, the distribution of values for forty-eight-hour urinary excretion is slightly skewed and for the other values which we have enumerated it is rather markedly skewed. For

[1] $\overline{M} \pm 2\sigma$ = the mean value plus or minus twice the standard deviation.

purposes of comparison we have estimated, by graphic fitting of cumulative frequency curves for various groups, a range of values estimated to include 95 per cent of the observations, which are labeled in the tables "estimated range." This range was arbitrarily chosen because it was considered that observations which fell outside it, even though normal, had better be considered as equivocal and uncertain for diagnostic purposes. The range arbitrarily chosen by Werner, Quimby and Schmidt, on the other hand, includes about 91 per cent of their observations on euthyroid subjects.

The distribution of euthyroid values for three groups is given in Table 6. The first is the observed range for the normal cases (group 1). The

TABLE 6. RANGE OF VALUES IN EUTHYROID PATIENTS

Group	No. of cases	48-Hour urinary excretion, per cent of dose		Extrarenal disposal rate, per cent per hour		No. of cases	24-Hour thyroidal accumulation, per cent of dose		Accumulation rate, per cent per hour	
		Estimated	Observed	Estimated	Observed		Estimated	Observed	Estimated	Observed
1.* Normal subjects	11	—	53–70	—	2.1–7.3	5	—	16.9–43.4	—	1.7–4.6
2–6 inclusive. Nonthyroidal conditions	71	45–83	40–86	1.5–8.0	1.2–8.9	38	5–46	4–60	0.8–7.2	0.5–7.8
10. Malignant thyroid tumors	75	45–80	42–83	1.3–6.9	0.8–8.0	55	7–43	0–45	0.5–5.8	0–7.5
Combined euthyroid group	157	45–82	40–86	1.3–7.6	0.8–8.9	98	6–45	0–60	0.5–6.8	0–7.8
Skanse—Normal subjects	110	51–81	53–86	—	—	—	—	—	—	—
Arnott and associates —Normal subjects	30	—	38–69	—	—	—	—	—	—	—
Werner and associates —Euthyroidism	57	—	—	—	—	—	10–35†	7–49	—	—
Mason and Oliver—Euthyroidism	25	—	—	—	5.5–12.0	—	—	—	—	—

* These numbers correspond to the group numbers in Table 2.
† Estimated range includes 91 per cent of observations.

estimated and observed ranges are given for groups 2 through 6 combined. Because of the possible relation between renal function and thyroidal iodine-accumulating function suggested by the data in Table 2, groups 7, 8 and 9 were omitted from this tabulation. Group 10, comprising 75 patients having malignant thyroid tumors, has been included. Because the data for these groups coincide so closely they have been combined as a total euthyroid group, the range of which will be employed as a basis for evaluation of hyperthyroid and hypothyroid states. Groups 11 and 12, which include euthyroid patients with endemic nodular goiters and colloid goiters, have not been employed in this summary because the values recorded suggest that there may sometimes be alteration of iodine-accumulating function in these conditions. The range of values in Table 6 may

not be identical with the normal range of a large series of healthy adults. Such data would be exceedingly useful to compare with these, and will undoubtedly be obtained if future improvement in tracer technics provides methods for exact in vivo and urinary measurements with small (1 to 10 microcuries) quantities of I^{131}. Regardless of what the true normal range is later found to be, however, the euthyroid range depicted probably describes optimal useful diagnostic limits for the indexes of radioiodine accumulation which we have employed. Our euthyroid series includes most, although not all, of the common conditions in which evaluation of the functional status of the thyroid is likely to be difficult and in which the basal metabolic rate is sometimes misleading.

Range of values in hyperthyroid and hypothyroid persons

In Table 7 are compiled the ranges of values encountered in the principal categories of thyroid conditions, compared with the euthyroid values discussed previously.[2] For each value, an "estimated range" is given, which is considered to include 95 per cent of the observations. In addition is listed the percentage of observed values which overlap the estimated euthyroid range. Data for basal metabolic rate in the same patients are also included, the comparable "normal range" being taken from the extensive study of Boothby, Berkson and Dunn (26). The range of basal metabolic rate which approximately includes 95 per cent of the normal population at all ages after 25 years is minus 13 per cent to plus 13 per cent.[3]

Exophthalmic goiter

It is evident that the radioiodine accumulation, however measured, is a sensitive method of separating patients who have exophthalmic goiter from euthyroid persons. It is surprising to find that forty-eight-hour urinary excretion is, from these data, as sensitive in this regard as the other values compared, in the respect that it yields a similar proportion of "false negative" results. In this series it is the most sensitive of the four

[2] The euthyroid group used as a standard for comparison with the others in the table is obviously heterogenous with respect to basal metabolic rate, a fact implicit in the selection of cases comprising it. The proportion of cases with basal metabolic rates outside the normal range is therefore a measure of the extent to which this group represents conditions in which the differential diagnosis of thyroid disease is not helped by determination of basal metabolic rate.

[3] The mean basal metabolic rate for any age is always expressed as zero; the standard deviation of this value for all adults of the Mayo Foundation Standard is 6.9 per cent; thus -13 or $+13$ per cent is within the $\overline{M} \pm 2\sigma$ range which represents 95 per cent of the observations; -14 or $+14$ per cent is outside it.

TABLE 7. COMPARATIVE RANGE OF VALUES IN THYROID DISEASES

Group	No. of cases	Basal metabolic rate		48-Hour urinary excretion		Extrarenal disposal rate		No. of cases	24-Hour thyroidal accumulation		Accumulation rate	
		Estimated range, per cent	Percentage within normal range (−13 to +13 per cent)	Estimated range, per cent of dose	Percentage within euthyroid range	Estimated range, per cent per hour	Percentage within euthyroid range		Estimated range, per cent of dose	Percentage within euthyroid range	Estimated range, per cent per hour	Percentage within euthyroid range
Euthyroidism	157	−25 to +34	49.0	45–82	—	1.3– 7.6	—	98	6–45	—	0.5– 6.8	—
Adenomatous goiter without hyperthyroidism	49	−21 to +20	86.0	22–86	79.6	0.3–13.5	81.6	27	2–73	80.0	0.5–11.3	76.0
Exophthalmic goiter	123	+ 9 to +70	4.8	3–54	5.7	4.0–80.0	8.1	61	28–89	18.0	2.5–60.0	14.8
Adenomatous goiter with hyperthyroidism	25	+10 to +58	8.0	10–74	48.0	0.5–26.0	44.0	13	16–78	38.4	0.5–25.0	30.7
Myxedema	46	−48 to − 8	13.0	60–90	76.1	0– 2.6	39.0	28	0–15	39.3	0– 1.3	28.6

indexes used, although statistically the percentage values indicating overlap with the euthyroid range are not significantly different from one another. With the technics here employed, in vivo methods appear less sensitive than urinary ones for the diagnosis of exophthalmic goiter. On the basis of the data in Table 7 alone, there is no significant difference in sensitivity of UE or ERDR with respect to the diagnosis of exophthalmic goiter. For reasons to be mentioned, however, the latter appears preferable. The finding that in vivo observations overlap more than urinary ones is most probably a reflection of the comparative inaccuracy of in vivo observations. Providing great care is taken with the collection of urine so that error resulting from loss of urine is minimized, urinary measurements are technically quite accurate, probably within 5 per cent. Even under ideal conditions, however, in vivo measurements may be in error by 15 per cent and perhaps more. Some of the sources of errors in in vivo measurements appear to be intrinsic and unrelated to the apparatus or to the technic employed: 1) the inability to measure accurately radioiodine in the neck but not in the thyroid; 2) the inability to determine accurately the effective center of radiation in the thyroid, or to evaluate the different geometric conditions resulting from variations in the size of the thyroid or the size of the neck; and 3) the inability to measure accurately the effects of absorption and scatter of radiation within the neck, which may also vary in different individuals having different dimensions.

The foregoing remarks about the comparative insensitivity of our own in vivo observations apply with equal force to those of Werner and associates, which coincide extremely closely with our own. The normal range which they have employed is less inclusive than the one which we have used, since it includes only 91 per cent of the observations in their euthyroid series. A cumulative frequency curve constructed from the data on twenty-four-hour thyroidal accumulation for 57 euthyroid cases in the series of Werner and associates discloses that the range estimated to include 95 per cent of the observations (so as to be strictly comparable with our data) is approximately 6 to 44 per cent. This is virtually identical with our own. It is not possible to calculate from the published table of Werner and associates the precise percentage of the "observations in hyperthyroidism" which fall within this range, but the value lies between 12 and 20 per cent. It is therefore evidently quite comparable to ours.

Of 123 cases of exophthalmic goiter only 5 (4.1 per cent) were found in which both urinary values fell within the normal range; of 61 cases in which in vivo data were also obtained only 3 (4.9 per cent) were found in which all values, urinary and thyroidal, fell within the normal range. Slight additional sensitivity is thus secured by obtaining multiple observations. Two of 123 patients who had exophthalmic goiter (1.6 per cent)

TABLE 8. RANGE OF VALUES IN CASES OF MILD OR OBSCURE EXOPHTHALMIC GOITER

Group	No. of cases	Basal metabolic rate		48-Hour urinary excretion		Extrarenal disposal rate		No. of cases	24-Hour thyroidal accumulation		Accumulation rate	
		Observed range, per cent	Percentage within normal range (−13 to +13 per cent)	Observed range, per cent of dose	Percentage within euthyroid range	Observed range, per cent per hour	Percentage within euthyroid range		Observed range, per cent of dose	Percentage within euthyroid range	Observed range, per cent per hour	Percentage within euthyroid range
1. Cases controlled with iodine alone	8	+ 5 to +40	37	15–45	0	12–39	0	5	44–65	12	9.7–29.6	0
2. Clinically mild; basal metabolic rate less than +20 per cent	20	+25 to +50	0	15–32	0	10–62	0	3	56–64	0	12–27	0
3. Difficult diagnostic problems	11	+ 5 to +20	18.0	19–39	0	8.5–38	0	15	43–82	6.6	6.6–32	6.6
4. Cases in equivocal category in which exophthalmic goiter was tentatively excluded	11	0 to +37	9.0	42–74	91.0	2.7– 8.2	91.0	5	23–37	0	2.6– 6.8	0

behaved as though myxedematous; that is, accumulated substantially no radioiodine. It is of particular interest that both of these had rather severe exophthalmic goiter and one was considered to be bordering on thyroid crisis at the time of study. The possibility could not be excluded that these patients might have received some interfering substance (such as iodine) about which we had no knowledge.

Value of radioiodine accumulation in the differential diagnosis of mild or equivocal exophthalmic goiter.—The recognition of frank severe exophthalmic goiter is usually sufficiently obvious to make any laboratory aid, including the basal metabolic rate, unnecessary except as confirmatory data for the record. It is in the mild examples of the condition that the clinical signs and symptoms become obscure and unreliable and the diagnostic problem is sometimes a difficult one which may lead the physician to rely heavily on laboratory aids. Several conditions have been discussed which sometimes resemble hyperthyroidism to some extent and may provide further confusion by associated elevation of the basal metabolic rate. These include nervous disorders, essential hypertension, cardiac disease and chronic alcoholism. It has been shown that radioiodine accumulation affords a useful means of ruling out hyperthyroidism in these conditions even in the presence of an elevated basal metabolic rate. The question of the diagnostic sensitivity of radioiodine studies is tested directly in mild or clinically equivocal cases in Table 8. The first group comprises 8 cases, in which the thyroid gland was small, and the disease was so mild that satisfactory control was achieved and maintained by the administration of strong solution of iodine (Lugol's solution) alone. The second group includes an additional 20 cases in which the disease was considered clinically mild and in which the basal metabolic rate was less than plus 20 per cent. The third group includes 11 cases, which had been considered as difficult diagnostic problems and provoked long and careful investigation before the diagnosis of exophthalmic goiter was acted on. This category includes cases of exophthalmic goiter complicated by chronic alcoholism, hypertension, anxiety states and the like.

The foregoing categories all comprise cases in which the diagnosis of exophthalmic goiter was subsequently confirmed by later events, usually the surgical findings, an unequivocal response to treatment or both. The fourth group comprises 11 cases in which the clinical symptoms and findings caused exophthalmic goiter to be a serious diagnostic consideration, but in which the weight of evidence led it to be tentatively excluded. In these instances, it was impossible to exclude the disease entirely in the light of subsequent events, usually because of failure of patients' symptoms either to disappear or to become sufficiently clear-cut as to be pathognomonic. These cases have been classified as equivocal, but the provisional

TABLE 9. COMPARISON OF VALUES BETWEEN ADENOMATOUS GOITER WITHOUT HYPERTHYROIDISM, ADENOMATOUS GOITER WITH HYPERTHYROIDISM AND EXOPHTHALMIC GOITER

Group	No. of cases	48-Hour urinary excretion		Extrarenal disposal rate		No. of cases	24-Hour thyroidal accumulation		Accumulation rate	
		Estimated range, per cent of dose	Percentage within goiter range*	Estimated range, per cent per hour	Percentage within goiter range*		Estimated range, per cent of dose	Percentage within goiter range*	Estimated range, per cent per hour	Percentage within goiter range*
Adenomatous goiter without hyperthyroidism	49	22–86	—	0.3–13.5	—	27	2–73	—	0.5–11.3	—
Adenomatous goiter with hyperthyroidism	25	10–74	96.0	0.5–26.0	94.0	13	16–78	92.0	0.5–25.0	88.0
Exophthalmic goiter	123	3–54	89.3	4.0–80.0	65.5	61	28–89	87.7	2.5–60.0	77.5

* "Goiter range" refers to the range of values in adenomatous goiter without hyperthyroidism.

clinical decision of the consultant (on evidence which at times did include the radioiodine tracer test) was that the patient did not have exophthalmic goiter. In those other problems in which the final diagnosis was unequivocal on evidence independent of the I^{131} study, the cases have been classified elsewhere, usually in groups 2 through 6 (Table 2).

On the basis of the data summarized in Table 8, it would appear that I^{131} accumulation is characteristically diagnostic even in mild cases of exophthalmic goiter or those which are difficult to recognize clinically. On the evidence presented, it is reasonable to suppose that perhaps most of the 11 patients comprising the equivocal group were correctly considered not to have exophthalmic goiter.

Adenomatous goiter with hyperthyroidism

When observations on hyperfunctioning nodular goiter are compared to those on euthyroidism, a much smaller proportion of cases than of cases of exophthalmic goiter are found to be separated by means of radioiodine studies and from a third to a half of the cases appear to be within the normal range, no matter what criterion is employed (Table 7). However, this is only part of the problem so far as the diagnostic use of radioiodine in cases of hyperfunctioning adenomatous goiter is concerned. Patients who have this condition are usually recognized on physical examination to have a palpable nodular goiter; the differential diagnosis is limited to the question of whether the patient is euthyroid or hyperthyroid. It was pointed out that the variability of the results of radioiodine tests in adenomatous goiter without hyperthyroidism, however measured, is greater than in other euthyroid conditions and this is further indicated in Table 7. The diagnostic value of radioiodine in the presence of nodular goiter therefore should be measured by the proportion of cases of adenomatous goiter with hyperthyroidism having values for I^{131} accumulation which are outside the range of values observed in adenomatous goiter without hyperthyroidism. The range of values in adenomatous goiter without hyperthyroidism is shown in Table 9. The ranges of values observed in cases of adenomatous goiter with hyperthyroidism and in cases of exophthalmic goiter are also shown, together with the proportion of these groups which overlap the range of values encountered in adenomatous goiter without hyperthyroidism.

On this basis it is evident that radioiodine tracer tests are of limited value at best, no matter how measured, for indicating the presence or absence of hyperthyroidism in cases of adenomatous goiter. This is particularly unfortunate, because the question of hyperthyroidism in elderly goitrous patients with cardiovascular disease is frequently both a critical

and a difficult problem. Comparison of exophthalmic goiter and adenomatous goiter without hyperthyroidism is less realistic, for in the majority of instances the character of the thyroid, as well as other clinical observations, would be such that this comparison would not arise; hence the more favorable contrast found between exophthalmic goiter and other euthyroid groups can be used.

Myxedema

In myxedema, the urinary radioiodine values are less useful diagnostically than they are in exophthalmic goiter (Table 7). All of the values are wanting so far as specificity is concerned. ERDR is much more sensitive than UE in hypothyroid persons but still overlaps the normal range in more than a third of cases. In vivo observations appear to be a little better, but not much. On the basis of in vivo studies it is, however, possible to divide myxedematous patients into two categories: 1) those who are athyrotic (at least with respect to I^{131} accumulation), and 2) those with reduced but not absent thyroidal function. In the first group, which in our series comprises about two thirds of the cases, the absolute lack of uptake constitutes a very useful diagnostic guide. In the second group, in vivo observations have only limited usefulness, overlapping the lower part of the euthyroid range very considerably.

Value of radioiodine tracer test in the differential diagnosis of myxedema.—Several somewhat paradoxic circumstances limit the diagnostic usefulness of radioiodine studies in hypothyroid conditions. These may be summarized as follows: 1) The normal range of radioiodine values overlaps that of myxedema to a considerable extent. 2) Certain thyroid conditions unassociated with myxedema have reduced radioiodine accumulation; these include nearly all patients with acute diffuse thyroiditis, some patients with Riedel's thyroiditis and a significant minority of patients having adenomatous goiter without hyperthyroidism. 3) In some cases certain systemic disorders appear to be associated with reduction of iodine-accumulating function. These include cardiac decompensation, renal insufficiency and Addison's disease, and the possibility exists that other conditions not yet surveyed may show similar reduction. 4) The ingestion of iodine or of organic iodine compounds by the patient, in some situations months before a tracer test, may markedly impair radioiodine accumulation. Antithyroid drugs have a similar effect. 5) Certain patients who have myxedema, notably those who have Hashimoto's thyroiditis, show normal radioiodine accumulation. On the basis of the foregoing difficulties, radioiodine has limited value in the diagnosis of hypothyroidism, but may be a useful adjunct to other diagnostic measures when such factors as the foregoing can be carefully weighed and considered.

Comparison of various measures of radioiodine accumulation

In the average case of exophthalmic goiter the behavior of radioiodine is so modified from the normal that any measure of it which is employed provides equally unequivocal information. To a limited extent the same is true in severe myxedema. The striking feature about the four measures of radioiodine accumulation which we have here compared is the fact that they are all so nearly equal to one another in diagnostic sensitivity.

However, the evaluation of sensitivity, in terms of the extent to which a diagnostic test overlaps the normal range, does not constitute complete appraisal of diagnostic usefulness. A diagnostic aid may be highly sensitive

TABLE 10. OCCURRENCE OF "FALSE POSITIVE" RESULTS IN 10 ILLUSTRATIVE EUTHYROID PATIENTS HAVING LOW RENAL EXCRETION RATES

Case	Diagnosis	Renal excretion rate, per cent per hour	Basal metabolic rate, per cent	48-Hour urinary excretion, per cent of dose	Extrarenal disposal rate, per cent per hour	24-Hour thyroidal accumulation rate, per cent of dose	Accumulation rate, per cent per hour
18	Cardiac decompensation	1.3	+37	16.8*	6.3	79.5*	5.0
19	Cardiac decompensation	1.1	+10	28.2*	2.4	42.7	2.2
20	Cardiac decompensation	2.4	+26	40.1*	2.4	27.3	1.9
21	Cardiac decompensation	1.8	−16	42.5*	1.6	18.5	1.2
22	Nephrosclerosis with uremia	0.7	0	19.7*	1.6	24.9	1.3
23	Essential hypertension	1.9	+23	21.5*	6.9	49.3*	4.4
24	Essential hypertension	1.9	+5	38.9*	2.5	26.1	1.7
25	Adenomatous goiter without hyperthyroidism	2.9	+9	31.0*	6.4	53.5*	5.5
26	Adenomatous goiter without hyperthyroidism	3.2	−1	42.9*	4.1	38.7	3.3
27	Adenocarcinoma of thyroid	3.3	+7	36.7*	5.7	39.7	4.0

* Values marked with asterisk are outside euthyroid range.

and still have limited practical usefulness if it is too nonspecific and provides too many falsely positive results. From the survey of conditions summarized in Table 2, as well as the data concerned with the effects of iodides and other interfering substances, it is obvious that all measures of radioiodine accumulation are comparatively nonspecific with respect to the diagnosis of hypothyroidism. It is equally obvious that all measures of radioiodine accumulation are comparatively specific with respect to the diagnosis of hyperthyroidism. In numerous individual instances, however, rates, such as ERDR or AR, more specifically exclude hyperthyroidism, giving correctly negative results when quantities such as UE and TA give false positive results. This is most likely to occur if for any reason the urinary excretion of iodide is impaired. Table 10 includes 10 cases illustrating this point; in all of these RER was low and UE was falsely positive. In 3 of the 10, TA was also falsely positive.

The comparative merits and shortcomings of the radioiodine values which have been compared in this study may be summarized in terms of diagnostic sensitivity, specificity, safety, technical difficulty and expense as follows:

1. Forty-eight-hour urinary excretion of radioiodine.—This test has the advantage of being technically simpler and therefore less expensive to perform than any other test of radioiodine which has been proposed. It is as sensitive a diagnostic measure of hyperthyroidism as any of the values compared in the respect that falsely negative results occur no more frequently than with the more complex procedures. Finally, measurement of a quantity of radioiodine in the urine, such as that in forty-eight hours, will always possess the considerable advantage of requiring the use of less radioiodine than other methods. In terms of radiation hazard it is thus the least objectionable method likely to be found. With equipment now available, forty-eight-hour urinary excretion can quite readily be determined with 5 or 10 microcuries of I^{131}. With apparatus likely to become available, it should be possible to make this determination with quantities as small as 1 microcurie, which is so small an amount as to make the question of radiation hazard a negligible one.

This test has the principal disadvantage of being the most indirect, and accordingly the least specific measurement of the four, both in the diagnosis of hyperthyroidism, and particularly in the diagnosis of hypothyroidism. False positive results are obtained frequently in conditions associated with impaired renal function and occasionally in patients without evidence of organic renal disease but in whom renal excretion of radioiodine is unaccountably impaired. Finally it has the technical disadvantage of being dependent on the co-operation of the patient in accurately collecting urine samples. Unless information can be obtained from patient or attendants, the value obtained for forty-eight-hour urinary excretion provides no means of determining if error in urine collection has occurred, and such errors can easily lead to falsely positive results suggesting hyperthyroidism.

2. Twenty-four-hour in vivo thyroidal accumulation.—In vivo observations have the principal advantage of providing direct information about the thyroid. In addition they do not require the direct co-operation of the patient and are not therefore subject to the errors associated with careless collection of urine specimens. Twenty-four-hour thyroidal accumulation is as sensitive in the diagnosis of both hyperthyroidism and hypothyroidism as any of the other tests compared, and is considerably more specific in regard to the latter condition than UE.

In our hands these advantages have not outweighed the principal disadvantage of intrinsic inaccuracy inherent in in vivo observations. More-

over, in vivo study has the disadvantage of requiring that the patient be brought to the apparatus or the apparatus to the patient. It requires more time and effort, is technically more difficult and therefore involves more expense than do urinary studies. TA has been found to be less specific than measurement of rates and in spite of the fact that it is a direct measurement of radioiodine in the thyroid, occasionally it is more misleading than indirect observation based on urinary studies, such as ERDR. Finally, in vivo measurements require larger quantities of radioiodine than do urinary studies alone; although technical refinements may reduce the quantity of radiation required, it is improbable that they will modify the comparative disadvantage of this technic in this respect.

3. Extrarenal disposal rate.—This test appears as sensitive a measure of hyperthyroidism or hypothyroidism as any of the methods compared. It is more specific than UE or TA in the diagnosis of hyperthyroidism and nearly as specific as TA in the diagnosis of hypothyroidism. There is reason to think that it provides a better approximation of the quantitative status of radioiodine accumulation than either of the foregoing procedures.

This test has one point of superiority over the others. It cannot be obtained without also measuring UE, RF, DR and RER. The net advantage of all of these is superior to any one of the tests being considered alone. For example, in the specific case of altered iodine-accumulating function associated with impaired renal function, analysis of the cumulative excretion curve is the only procedure which indicates correctly the direction and magnitude of altered thyroid function and in addition provides a measure of a probable basis for it (in the reduced RER). Conversely, when impaired radioiodine accumulation is encountered where one did not expect it, the finding of a normal RER excludes one important nonthyroidal explanation for the observation.

ERDR has the disadvantage of requiring the careful collection and analysis of six to eight specimens of urine, compared with one or two in the case of UE. In addition the data involve some special calculations, which are not, however, particularly onerous on a routine basis. ERDR thus entails more work for the laboratory and on this account is a more expensive procedure to carry out. Moreover, it is more dependent on the co-operation of the patient or attendants, since the accuracy with which a urinary excretion curve can be obtained depends as much on the precision and completeness with which specimens are collected as on the analytic technic employed in the laboratory to measure the specimens. It requires somewhat more radioiodine to be used than is needed for accurate estimation of UE, but less than is required for in vivo studies.

Several investigators (3, 5, 8, 27) have preferred not to use ERDR, because, as we have pointed out, the premise on which the calculations for

ERDR are based is oversimple and at best only a first approximation to the complex relationships involved. Objection has also been raised to the fact that the observations fit a simple exponential relationship for only a limited time, and during this interval they do not always fit a straight line with complete precision. We have not found these considerations to be serious disadvantages. We have found it impractical to make use of the more complex and perhaps more correct mathematical calculations suggested by Oddie (18), and have been impressed by the extent to which the simple calculations that we have used appear to fit the facts when tested in a variety of ways (28). Data based on averaging, or involving a straight-line relationship between several observations, as is the case with ERDR, may be less subject to technical or biologic sources of variation than any one observation. Furthermore, a peculiar advantage to be gained by using the cumulative radioiodine excretion curve from which ERDR is calculated is noted by Mason and Oliver (11): "Any gross variation of one sample from the mean curve was found always to result from an error in urine collection, so that inspection of the curve provided a useful check on the accuracy of the collections."

4. Accumulation rate.—This test possesses the advantages described for ERDR and in addition the advantage of being directly concerned with the thyroid. It is thus less likely than ERDR to be affected by differences in the quantity of radioiodine excreted in feces or sweat, or fixed in other tissues than thyroid. Such factors have not appeared to be of major importance, but nevertheless they should make AR theoretically at least the most quantitatively correct of the values which we have compared.

AR has the disadvantage of being no more accurate than the in vivo observations on which it is based, and when determined by the indirect method which we have used, it may be considerably less accurate in hyperthyroid patients. As done by any method, it would be the most arduous and time-consuming, therefore expensive, procedure of the four, since it would require either multiple in vivo measurements, which would be costly on any scale, or multiple urinary observations plus one or two in vivo observations as we have done. AR requires, as does TA, that more radioiodine be used, in order to get sufficient counts, than is the case with urinary measurements. Excepting in the case of patients with impaired iodine-accumulating function, it is our impression that in vivo observations possess no advantages over urinary observations.

5. Other measures of thyroidal iodine accumulation.—Various investigators have proposed other measures of thyroidal iodine accumulation than those that we have employed. These may be briefly compared as follows:

Quantity of Radioiodine Excreted in the Urine.—Skanse (5) has ob-

served that the urinary excretion for seventy-two or ninety-six hours affords a better index of hypothyroid conditions than does forty-eight-hour excretion, as does the excretion during the interval from twenty-four to forty-eight hours after administration of the dose. Mason and Oliver (11) have suggested the use of the quantity of radioiodine excreted in the urine between six and twenty-four hours after administration of the dose for evaluation of hyperthyroid states. Arnott, Emery, Fraser and Hobson (3), on the other hand, have preferred to compare the quantity excreted between twelve and twenty-four hours after administration of the dose. Both of these tests would appear to possess some minor advantages over forty-eight-hour urinary excretion, in separating hyperthyroid persons from normal ones.

Thyroidal Iodide Clearance.—Several studies (14, 15, 17) suggest that thyroidal iodide clearance, expressed in the same way as renal clearance values, may be a more explicit and quantitative measure of thyroidal iodine accumulation than any of the methods that we have surveyed. This procedure requires as a minimum two in vivo thyroidal observations and two specimens of serum obtained at the same times for measurement of inorganic radioiodide; and for maximal accuracy more than two observations are required. We have been deterred from applying this procedure on a routine basis entirely by practical considerations. Until the present time, the technical difficulties involved in accurate measurement of serum inorganic radioiodide have precluded large-scale study of this test. With the development of more efficient methods for rapid measurement of radioactivity, determination of thyroidal iodide clearance may become practically feasible. When it does, both our experience and that of Pochin (14) suggest that it may prove superior as a diagnostic aid to other measures such as ERDR and AR.

Accumulation Gradient.—Astwood and Stanley (12) have devised an empirical method for comparing the increase in thyroidal radioiodine with time. The value which they obtain is called "accumulation gradient," and is equivalent to accumulation rate excepting that it is expressed in arbitrary units. This method has the advantage of providing a measure of thyroidal accumulation after a few in vivo observations which need not be expressed in absolute terms. Furthermore, the value can be calculated within a few hours, whereas ERDR or AR require one to three days of observation. The serious disadvantage of accumulation gradient is that this value is expressed in arbitrary units which depend on the dose of radioiodine given in absolute terms, the individual characteristics of the counter tube, and the exact geometric relationship of tube to thyroid which is employed for counting. On this account, values obtained in one laboratory cannot with safety be compared with those observed elsewhere.

Other aspects of thyroid function measured with I^{131}

Finally it deserves to be emphasized that the thyroidal function here discussed, namely iodine accumulation, is not the only aspect of thyroid activity which can be evaluated in patients with radioiodine. At least two others are receiving attention: 1) The concentration of radioactive protein-bound iodine in the blood after administration of a tracer dose of I^{131} (16, 29). This test, however measured, should prove to be principally an index or measure of the turnover rate of circulating hormone. 2) Evaluation of the ability of the thyroid to concentrate inorganic iodide after exhibition of an antithyroid drug (23) or large quantities of iodide (30). This aspect of thyroid function, called the "thyroidal iodide trap," is distinct from radioiodine accumulation. It is possible that these procedures may prove to have important diagnostic value; this cannot be inferred or deduced from the data here presented but will require independent evaluation in a suitable series of patients.

Radioiodine-accumulation tests versus basal metabolic rate

It is appropriate to compare the radioiodine-accumulation tests with the basal metabolic rate as a diagnostic criterion of thyroid activity. It is not possible to make a purely objective comparison using the data obtained in this series, first, because the basal metabolic rate considered in relation to other clinical criteria was part of the basis on which the cases were diagnosed in some instances. Second, a number of the euthyroid categories were deliberately chosen for study because they represented situations in which the basal metabolic rate commonly provides misleading information.

Basal metabolic rate has been criticized as a diagnostic aid on several grounds: 1) because it is not a direct measure of energy consumption, and only indirectly an index of thyroid function; 2) because its accuracy and dependability depend very much on the co-operation of the patient; 3) because the basal or postabsorptive state, the necessary condition for determinations of basal metabolism, is difficult to approach; 4) because there are numerous subtle and disastrous technical difficulties in the determination; 5) because some patients who have hyperthyroidism or hypothyroidism are found whose basal metabolic rate is within normal limits (a measure of its insensitivity); and 6) because some patients without thyroid disease have basal metabolic rates above or below the normal range (a measure of its lack of specificity, *see* groups 3, 4, 5, 6, and 7, Table 2). The fact is of course that the careful clinician takes into account all these factors in evaluating the basal metabolic rate. On this account, in spite of these shortcomings it has, from its introduction to the present time, proved the most useful of the laboratory measures commonly available for the diagnosis of thyroid disease.

It appears that interpretation of radioiodine tests is beset with fully as many pitfalls and complexities as is interpretation of the basal metabolic rate even though they are different in kind. Our experience with radioiodine has not led us to the conclusion that it is any more sensitive or more specific, or any less subject to technical error or misinterpretation than the basal metabolic rate. By accumulating a large series of normal values it would be possible to define more precisely the normal range of radioiodine values, but a priori it appears unlikely that this will improve the diagnostic efficiency of these tests to any significant extent. Moreover with present technics radioiodine tests have one important disadvantage: they expose the patient to considerable quantities of radiation. Both on this account and because of the difficulties enumerated, we should prefer the basal metabolic rate to a radioiodine tracer test, if one were compelled to rely on onlv one diagnostic procedure.

We do not believe that the basal metabolic rate is destined to be supplanted. Radioiodine accumulation is a measure of an altogether different aspect of thyroidal activity from that reflected by the basal metabolism. Radioiodine studies have proved most useful thus far as an adjunct of considerable aid in difficult diagnostic situations in which the basal metabolism is difficult to interpret or technically unreliable. In our opinion, radioiodine will have its chief value in this respect, as well as by providing an additional method for evaluating the status of the diseased thyroid, which when employed with basal metabolic rate, serum protein-bound iodine and other measures of thyroidal activity should eventually lead to better understanding of thyroid disease.

SUMMARY AND CONCLUSIONS

The radioiodine-accumulating function of the thyroid has been studied by tests of several types in 790 patients who had various conditions. It was found to be significantly increased in patients who had exophthalmic goiter, or adenomatous goiter with hyperthyroidism, and significantly reduced in patients who had myxedema.

Significant elevation of radioiodine accumulation was also encountered in some patients who did not have hyperthyroidism. These included patients who had adenomatous goiter without hyperthyroidism, colloid goiter, hyperplastic thyroid nodules and thyroid hyperplasia resulting from antithyroid drugs.

Significant depression was encountered in many situations unaccompanied by clinical hypothyroidism. These included renal insufficiency, cardiac decompensation, Addison's disease, acute diffuse thyroiditis and Riedel's thyroiditis. Depression of iodine accumulation as measured with radioiodine occurred when inorganic iodine had been ingested within a week. It

was observed many months after administration of gallbladder dye. Antithyroid drugs, as well as other organic iodine compounds including desiccated thyroid, were also found to interfere with radioiodine accumulation. In some instances relative or absolute suppression of radioiodine accumulation which could not be explained was encountered in normal or hyperthyroid patients.

Normal values for radioiodine accumulation were observed in most cases of adenomatous goiter without hyperthyroidism, in about half the cases of adenomatous goiter with hyperthyroidism, in a few cases of exophthalmic goiter and in some cases of myxedema. Patients found to have Hashimoto's thyroiditis associated with clinical myxedema characteristically had normal values for radioiodine accumulation.

In spite of the foregoing, measurement of radioiodine accumulation by any one of several means was found to be a highly efficient diagnostic tool for separating more than 90 per cent of cases of exophthalmic goiter from normals. It was found to be comparatively inefficient as a method for establishing the presence or absence of hyperthyroidism in cases of adenomatous goiter. Radioiodine accumulation was found to be less useful in the diagnosis of myxedema, providing unequivocal evidence of hypofunction in about half the cases and equivocal evidence in the rest.

Four methods for measuring radioiodine accumulation were compared. These include 1) the measurement of the quantity of radioiodine excreted in the urine within forty-eight hours after its administration; 2) determination of extrarenal disposal rate from analysis of the curve of urinary radioiodine excretion; 3) in vivo measurement of the quantity of radioiodine accumulated in the thyroid twenty-four hours after administration of the dose, and 4) determination of an in vivo accumulation rate. All four values proved similar in diagnostic sensitivity. Extrarenal disposal rate provided the clearest picture of the state of radioiodine function, particularly in situations complicated by altered renal function. In vivo observations provided more accurate information in the presence of reduced or absent iodine accumulation than did urinary observations, but in other circumstances were less efficient, possibly owing to the intrinsic inaccuracies of in vivo measurements. Determination of forty-eight-hour urinary excretion proved to be a less specific measure of uncomplicated hyperthyroid states than the others, and in some conditions it provided inexact and misleading information. It was, however, the simplest and least expensive of the procedures employed.

Measurement of radioiodine accumulation was considered to be comparable but not superior to determination of basal metabolic rate as a measure of thyroid function. In view of the difficulties and hazards which

attend the use of radioiodine it appears likely that it will supplement rather than supplant other diagnostic aids.

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GLYCOGEN IN HUMAN TESTICULAR BIOPSY MATERIAL

PRELIMINARY REPORT

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THE study of intermediary carbohydrate metabolism is the pathway to increasing our knowledge of the metabolism of many other substances of fundamental biologic importance. It has been shown that sex hormones, among others, are able to influence such phenomena through the mobilization of some enzymatic systems. Biochemical and histochemical studies have demonstrated that human endocrine sterility is often associated with endometrial abnormalities of phosphorylase activity, and in the amount and distribution of alkaline phosphatase and glycogen (Zondek and Hestrin (1), Hughes (2), Atkinson and Engle (3), Arzac and Blanchet (4)). The intimate relationship between the physiology of human spermatozoa and carbohydrate metabolism has been well stressed by McLeod (5) and others. Wislocki (6) has recently found seasonal differences in the content of polysaccharides in the testes of deer. However, although some recent histochemical investigations have been made on the lipids of the human testis (Nelson and Heller (7)), so far as the author knows, the possible modifications of the amount and distribution of glycogen in this organ have not been investigated in abnormalities of the testes associated with sterility.

The purpose of this paper is to summarize the findings on the glycogen content, revealed histochemically, of human testicular biopsy material obtained because of azoospermia and sterility of the male partner.

METHODS

Testicular biopsy specimens, obtained from 17 sterile patients following the technique described by Hotchkiss (8), were immediately fixed in 96 per cent alcohol, then transferred to alcohol-formol-acetic, embedded in paraffin, and after sectioning at 6 microns, mounted and stained by different methods, For the demonstration of glycogen the following procedures were applied: periodic-acid-leucofuchsin according to Lillie (9) and McManus (10); periodic-acid-carbolfuchsin (Arzac (11)), and "indirect" and "direct" silver reactions according to Arzac (12), and Arzac and Flores (13). The author's hematoxylin, light green, picric acid, and polychrome mixtures (unpublished) were used as counterstains. Control slides were digested

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with saliva from thirty to one hundred and eighty minutes at various temperatures.

The samples of tissue studied can be grouped as follows:

Tubular degeneration	10
Tubular plus Leydig cell degeneration	2
Normal testes	5

If obtained by necropsy, histochemically normal testes are practically impossible to secure because of the rapidity of glycogenolysis. Therefore, the biopsy specimens were considered normal as far as their glycogen content was concerned if no histologic abnormalities existed.

RESULTS

Normal testes.—Besides the expected histologic structure, a definite although slight reaction for carbohydrates was obtained in the seminiferous tubules. It appeared as very fine granules diffused throughout the cytoplasm of Sertoli cells; concentration was greater toward the base and near the borders of other tubular cells. The tubular lumens were practically free of secretion. After digestion with saliva, the aforementioned granules disappeared; but diffused throughout the background a faint color could be demonstrated with periodic-acid-fuchsin techniques but not with silver methods. No part of the spermatic cells in any state of maturation showed glycogen. Vascular reticulum and basal membranes were also demonstrated

Pathologic testes.—Since a description of the well known histologic abnormalities of the hypoplastic testis is unnecessary for the purpose of this report, the findings can be summarized as follows: a) The apparent amount

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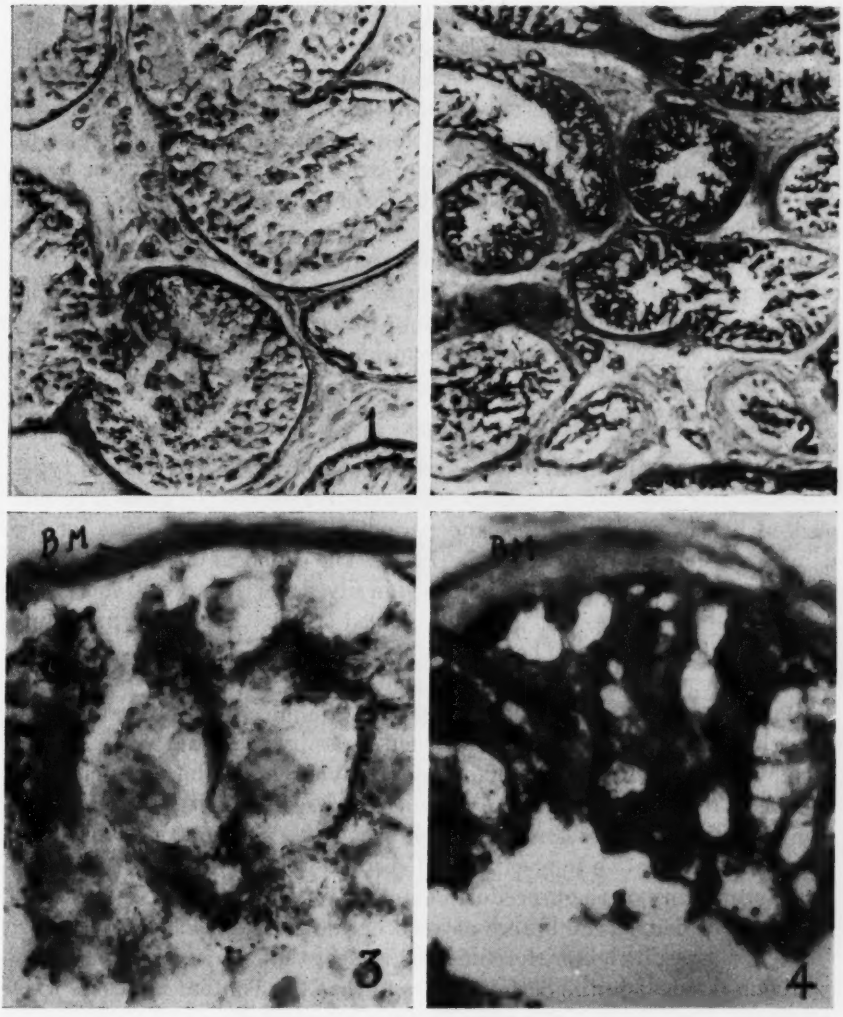
FIG. 1. Normal testis. A small amount of glycogen is seen in the cytoplasm of the Sertoli cells. It appears as small, black spots near the basal membrane, which is also stained along with arterial elastine. The periodic-acid-carbolfuchsin histochemical method was used, with no counterstaining. ×160.

FIG. 2. Section of testis, showing tubular degeneration. Great abundance of glycogen is clearly evident in the cytoplasm of the Sertoli cells, which were the only cells present in the tubules of this specimen. Note the small size of the tubules and the widening and diffuse staining of the basal membrane as compared to the normal testis in Figure 1. The periodic-acid-carbolfuchsin histochemical method was used, with no counterstaining. ×160.

FIG. 3. Photomicrograph of a fragment of the normal testis shown in Figure 1, taken at 400 diameters and amplified to demonstrate the fine granules of glycogen. "B M" indicates basal membrane of the tubule.

FIG. 4. Photomicrograph of a fragment of the hypotrophic testis shown in Figure 2, taken at 400 diameters and amplified. The masses of glycogen filling the cytoplasm of the Sertoli cells are evident. "B M" indicates basal membrane of the tubule.



FIGS. 1–4

or concentration of glycogen contained in individual tubules was always greater than normal in all of the pathologic specimens studied and increased roughly according to the degree of hypoplasia. However, when atrophy was extreme and hyalinization of the tubules complete, no glycogen was seen inside. This was true, whatever the developmental status of the Leydig cells. b) As in normal cases, no glycogen was present in the spermatic component of the testis; it seemed to be confined to the cytoplasm of the Ser-

toli cells when spermatogenesis reached relatively advanced stages. The tubular lumens or the intercellular spaces, however, showed rather considerable quantities of digestible carbohydrate in some of these instances and in those cases in which only spermatogonia and/or Sertoli cells were present in the tubules. Often the distribution seemed to be the reverse of normal: that is, more glycogen existed near the lumens than in the basal zones. It manifested itself as frequently coalescing granules and masses of different sizes.

Figures 1, 2, 3 and 4 are photomicrographs which illustrate the difference of glycogen content between normal and hypoplastic testes. These figures are highly contrasted in order to bring out the positive reactions. As no counterstaining was used, the nuclei in the background are practically imperceptible.

COMMENT

Although there is a difference of relative selectivity between both types of techniques, a common background seems to exist for the general results elicited by chromic-acid-silver and periodic-acid-fuchsin reactions for the demonstration of carbohydrates in tissues. The chemical mechanism of the oxidative effect of the chromic acid used in silver reactions is still somewhat obscure. Nevertheless, it is generally agreed that both types of procedure are aldehyde reactions. Therefore a positive result, especially when obtained with methods using periodic acid, is indicative of the presence of carbohydrates containing the 1, 2, glycol grouping in unsaturated form (Hotchkiss (14)). This means that such a positive result may be elicited by a variety of substances like mucin, glycogen, hyaluronic acid, and others, that are present in many tissues, and several of them almost certainly in the human testis. However, when the reaction of a substance changes from positive to negative if digestion with saliva precedes the performance of any of the procedures employed in this study, the substance may be considered as an hexose polysaccharide of the glycogen type.

From the results herewith reported it is clear that the adult human testis contains glycogen in the Sertoli cells, and that this content increases when a process of tubular hypofunction becomes established.

That this increase is absolute or relative cannot be definitely decided from the present data. In fact the amount of any substance contained in any organ may be large either because of excess production and storage, or because of lack of elimination and/or utilization. In this case, it could be assumed that the presence of relatively small amounts of glycogen in the normal testis may be sign of an active utilization that leaves no chance for storage. This active utilization could be related to the spermatogenetic process of the tubule or to some other function. On the other hand, the ex-

cess of glycogen in the tubules of hypofunctional organs may be caused either by: a) non-utilization, in which case the glycogen represents a chemical "debris" trapped in the tubules, or b) glycogen continues to be secreted as a nutrient which perhaps takes part in the intermediary metabolism associated with the formation of the fibrous tissue that ultimately obliterates the whole tubule in the hyalinization process connected with atrophy. The weakly positive periodic-acid-fuchsin reaction after digestion with saliva (light color diffused in background) may be interpreted as indicating the existence of a different carbohydrate, which probably formed part of some mucoprotein or glycoprotein. It almost certainly cannot be originated by lipidic carbonyls because alcoholic fixation and the other steps of paraffin embedding technique exclude this possibility. Neither can it be attributed to technical artifact, as this result does not appear when pre-oxidation is omitted.

SUMMARY

Histochemical reactions for carbohydrates, with special emphasis on glycogen, have been studied in biopsy specimens of the human testis in 17 cases of male sterility. It was found that normal specimens contain appreciable but moderate quantities of glycogen in the cytoplasm of the Sertoli cells and that the glycogen increases according to the degree of the hypoplastic process. No glycogen was present in other cells of either the normal or pathologic specimens. In complete atrophy, there was practically no glycogen. The possible significance of the findings is discussed.

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A STUDY OF A FAMILY OF GOITROUS CRETINS*†

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A patient with cretinism encountered in an iodine-deficient area usually has an enlargement of his thyroid gland (1). Microscopically it may show all degrees of nodularity, hyperplasia and involution (2). Unless completely degenerated, such a gland might be expected to have a normal or increased avidity for iodide and to bind it readily into an organic complex. By contrast, sporadic cretinism is usually not associated with goiter; there may be only a fibrous remnant to mark the site of the gland. Little or no accumulation of radioactive iodine can be demonstrated in the gland of such a patient (3). Much more rarely one encounters a cretinous subject who is clearly not deficient in iodine, who has been exposed to no known goitrogen, and yet who shows striking enlargement of his thyroid gland. Hamilton and associates (3) refer to 2 classic cases. Following the administration of radioactive iodine abnormally large collections of this material were noted in the thyroid glands of these patients. Two cretin brothers with goiter were studied by Lerman, Jones and Calkins (4). Histologic examination of biopsy specimens demonstrated areas of intense hyperplasia. These patients concentrated 87 per cent and 58 per cent of tracer doses of radioactive iodine in the region of their thyroids. One had the low concentration of 0.07 milligrams per cent of protein-bound iodine in the removed thyroid tissue. These findings suggested that the thyroids of these patients were unable to utilize iodine.

Lerman, Jones and Calkins (4) mentioned histologic studies of a gland removed from a third patient who was cretinous. The present investigation concerns studies of the function of the thyroid glands of 4 siblings of this patient. The parents of these children are intelligent and productive people who show no evidence of goiter or cretinism. They have always lived near the sea coast of Massachusetts. Both are said to be half Indian and are first cousins. Their first 3 children developed normally. The 4 succeeding siblings are all cretinous.

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This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1951.

Case I

Mildred E., *MGH Unit #357137,* a 16-year-old female child, was admitted to the hospital on May 12, 1949, because of difficulty in breathing. She was thought to be normal until about 6 months of age, when she seemed to be developing slowly. A physi-

FIG. 1. Case I, Mildred E., aged 16 years. Cretinism was recognized at the age of 1 year. The goiter was first noticed at 7 years of age. The removed tissue weighed 97 grams.

cian assured the mother that all was well, in spite of the fact that 2 older siblings were already recognized as cretins. Not until she was 2 years old was thyroid replacement therapy prescribed. At that time she showed no inclination to walk or sit up. From then until admission she was given desiccated thyroid sporadically. There were intervals when the family was unable to purchase the medication. Her general health, except for measles, had always been fairly good. She had never walked and had indicated her

wishes by guttural sounds. She was unable to feed herself, though her appetite was excellent. She was troubled by constipation, and was entirely incontinent of urine and feces. When the patient was 7 years old a mass was first noticed in her throat. This mass slowly increased in size until the time of admission.

Physical examination: The temperature was 99.8, respirations 25, and the blood pressure 110 systolic and 70 diastolic. The pulse varied from 80 to 120, depending on her mood. Her height was 112 centimeters and her weight was 30 kilograms. She presented a remarkable appearance (Fig. 1). The hair was black and slightly coarse. The skin was dry, cool, coarse, and had a curious spongy elasticity. The eyes were normal except that conjugate movements were not always present, but there seemed to be no specific pattern to this. The bridge of the nose was depressed. The lips were thick and protuberant. The thyroid was enlarged to about five or six times normal size, nodular, and firm. A bruit and thrill were present. The skin temperature was noticeably warmer over the gland than elsewhere. Examination of the heart and lungs revealed nothing abnormal. There were no abdominal masses. Pubic hair was scanty and axillary hair was lacking. Reflexes were diminished but present.

Behavior pattern. The patient made only guttural sounds or screamed when provoked. She sat up but was unable to stand. She did not feed herself. She was incontinent of urine and feces. She was fairly docile and cooperative after she became accustomed to her strange surroundings. She was much more manageable when not taking desiccated thyroid.

Laboratory data: The hemoglobin was 13.1 grams per 100 cubic centimeters. The white blood cell count was 12,600 with 68 per cent polymorphonuclear cells. Urinalysis gave normal findings except for many white blood cells. The chest was normal on x-ray examination. The trachea was narrowed and compressed from the right in the region of the enlarged thyroid gland. Bone age by Todd standards was 13 and 9/12 years. The serum protein was 7.4 grams per cent and the cholesterol was 212 milligrams per cent. No follicle-stimulating hormone was found in the urine. Serum alkaline phosphatase was 9.4 Bodansky units per cent. Determinations of 17-ketosteroids and 11-oxysteroids, made in the laboratory of Dr. Nathan Talbot, were 0.45 milligrams per 24 hours and 0.07 milligrams per 24 hours respectively. A urine culture grew abundant gram negative rods consistent with *E. coli*. The fasting blood sugar was 102 milligrams per cent. The blood nonprotein nitrogen was 34 milligrams per cent and the serum calcium was 9.4 milligrams per cent. The serum vitamin A level was 1.7 units and carotinoids 2.2 units per cubic centimeter, while the patient was taking thyroid. A Thorn test with epinephrine showed a fall of 61 per cent in the circulating eosinophils. It was not possible to obtain a basal metabolic rate. A determination of the protein-bound iodine of the blood was 1.02 micrograms per cent. She had received no thyroid medication for six weeks.

Subsequent course: On July 7, 1949, a subtotal thyroidectomy was performed. The thyroid tissue which was removed weighed 97 grams. Transient tracheal obstruction required a temporary tracheotomy. Convalescence was uneventful and the patient has returned to her home. Her parents are delighted with the cosmetic result.

Pathologic examination, by Dr. Austin Vickery: (Fig. 2) "The microscopic picture is of particular interest, for in addition to evidence of involution and atrophy there are distinct nodules composed of typical hyperplastic thyroid follicles. These acini are irregular in outline, showing epithelial inbuddings into their tortuous luminal spaces and are composed of cuboidal or columnar thyroid cells. Colloid is sparse but when present often reveals scalloping of its peripheral margins. These described foci of hyperplasia are intermingled with other regions or nodules exhibiting a wide range of partial

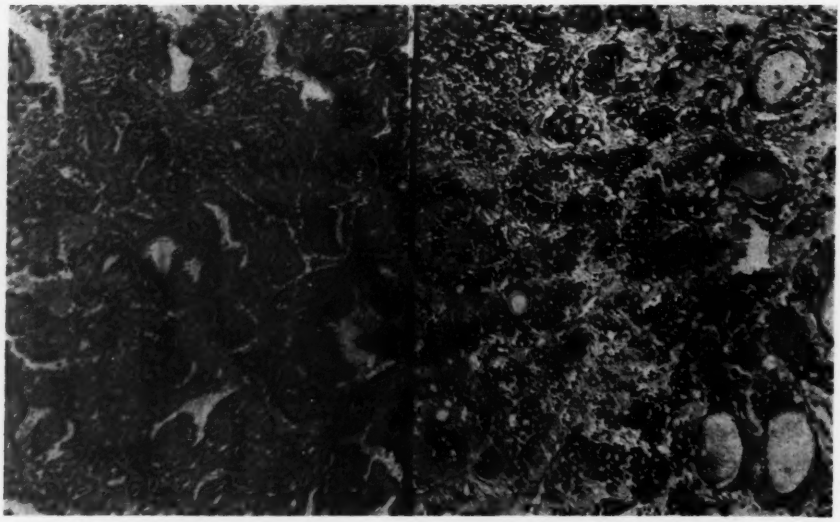

FIG. 2. Case I, Mildred E. Section of two areas of thyroid tissue showing intense hyperplasia on the left and disorganization of cellular pattern and replacement fibrosis on the right. For description, *see* text.

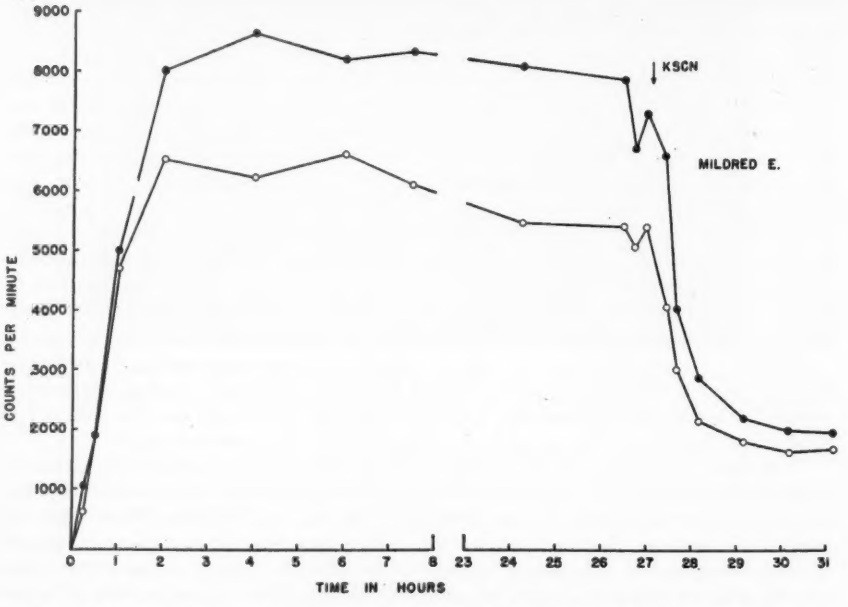

FIG. 3. Radioactive iodine accumulation and discharge in Mildred E., Case I. At

to complete involution with replacement fibrosis. There are many areas reminiscent of the 'fetal adenoma' histological pattern."

Tissue chemistry: Chemical analyses of the tissue removed at operation were made by Dr. Douglas Riggs. Thyroid inorganic iodide was 29.3 micrograms per cent and protein-bound thyroid iodine was 10.4 micrograms per cent.

Radioiodine studies: When the patient had been without thyroid medication for three weeks, a tracer dose of 100 microcuries of radioactive iodine was given. Radioactivity was recorded by a Geiger-Müller hand counter in contact with the skin. The radioactive iodine accumulated in the gland and reached a plateau in less than two hours (Fig. 3). During the next twenty-four hours counts over the gland declined slowly. Twenty-seven hours after administration of the radioiodine, 1.0 gram of potassium thiocyanate was given by mouth. This was followed immediately by a striking and rapid decline in the counts. At the end of two hours counts had fallen to 25 per cent of the previous level.

Case II

Charles E., *MGH Unit #357135* (Fig. 4), a 23-year-old male, was admitted to the hospital on September 26, 1949, because of increasing difficulty in breathing. At the time of delivery the obstetrician reported to the patient's mother that the child did not seem normal. Because he breathed noisily he was seen by a pediatrician at the age of 3 months. The pediatrician started thyroid medication. This was continued sporadically until a few months before hospital admission. He developed very slowly, beginning to walk only at the age of 16 years. Recently he had begun to speak a few guttural words. He finally learned to feed himself. When he was 13 years old, about the time puberty began, his mother first noticed the presence of a nodular mass in his neck. From that time until admission this gradually increased in size. Several months before admission he began to have difficulty in breathing. Otherwise he had always been quite well except for measles, whooping cough, chicken pox and several respiratory infections diagnosed as bronchial pneumonia.

Physical examination: The temperature was 98.2, the pulse 90, and the respirations 24. The blood pressure was 94 systolic and 64 diastolic. His height was 133 centimeters and his weight 43 kilograms. His head was large. The hair was black and slightly coarse. The skin was darkly bronzed, coarse, a little dry, and quite cool. It was loose and had the same curious elasticity of his cretinous siblings. The eyes were normal. The bridge of the nose was depressed, the lips full and protruding. The tongue was only slightly increased in size. The thyroid gland was huge and nodular, and the overlying skin was warm. There was a loud bruit and thrill. Examination of the heart, lungs and abdomen showed nothing abnormal. The patient had a normal size phallus and a normal amount of pubic and axillary hair. The testes were in the scrotum, were firm and slightly smaller than normal. The rectum was normal on examination. The reflexes were diminished.

Behavior pattern: After the patient became acclimated to the ward he was jovial and easy to deal with, but quite resistive to any force. When receiving thyroid he was able to say three or four words, but he did not speak when he was not taking thyroid.

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zero time, a tracer dose of 100 microcuries of radioactive iodine was given by mouth. The open circles are net counts per minute over the right side of the gland; the closed circles are net counts per minute over the left side of the gland. One gram of potassium thiocyanate was administered by mouth at the twenty-seventh hour.

He was incontinent of urine and feces. He recognized his mother. When taking thyroid he was able to walk in a curious lumbering fashion.

Laboratory data: The hemoglobin was 10 grams per 100 cubic centimeters. The white blood cell count was 8,600 with 73 per cent polymorphonuclear leucocytes. Urinalysis gave normal findings. X-ray examination showed a normal chest. There was narrowing

FIG. 4. Case II, Charles E., aged 23. Cretinism was recognized at the age of 3 months. Enlargement of the thyroid gland was first noticed at 13 years of age. Administration of desiccated thyroid was sporadic. The gland weighed 497 grams when excised.

of the trachea at the thoracic inlet. X-ray examination of the skull showed the sella to be at the upper limits of normal in size. The serum cholesterol was 272 milligrams per cent, the carotinoids 1.8 units per cubic centimeter, and the vitamin A level 0.2 units per cubic centimeter. The bone age corresponded to approximately 18 years by Todd standards. A serologic test for syphilis gave negative results. The protein-bound iodine of the serum was zero.

Clinical course: On October 11, the patient underwent a subtotal thyroidectomy.

The thyroid tissue which was removed weighed 497 grams, He withstood the procedure well and his convalescence was uneventful. His subsequent course has been unremarkable. An excellent cosmetic result was achieved.

Pathologic examination, by Dr. Austin Vickery: (Fig. 5) "The majority of sections reveal little or no evidence of normal thyroid architecture. Fibrosis is a conspicuous feature throughout, varying from total replacement of parenchyma to a diffuse thickening of the interstitial connective tissue. Where thyroid epithelial elements are present they are largely in solid cords and clusters of small to medium cells with small round regular nuclei and pale to vacuolated cytoplasm. Only an occasional actual follicle is seen in these areas, sometimes containing pale basophilic colloid. The zones of cells arranged in solid cords with a paucity of acinar formation are characteristic of adenoma-

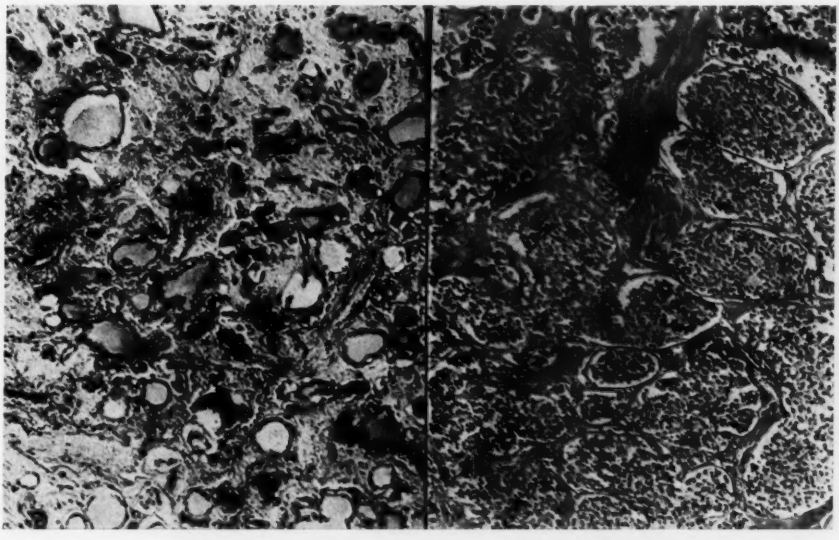

FIG. 5. Case II, Charles E. Sections of two areas of thyroid tissue showing marked fibrosis and disorganization of cellular pattern on the left, and paucity of acinar formation characteristic of so-called "fetal adenoma" on the right. For description, *see* text.

tous tissue of the so-called 'fetal adenoma' type with secondary degenerative changes and replacement fibrosis. In other regions various nodules showed different phases of parenchymal atrophy with scattered groups of disintegrating cells and nuclei interspersed in a fibrous or acellular amorphous stroma."

Tissue chemistry: Chemical analyses of the tissue removed at operation were made by Dr. Douglas Riggs. Thyroid inorganic iodide was 173 micrograms per cent and thyroid protein-bound iodide was 15 micrograms per cent.

Radioiodine studies: Five months after the patient had last taken desiccated thyroid he was given a tracer dose of 100 microcuries of radioiodine (Fig. 6). The radioactivity accumulated rapidly over the thyroid gland. At the same time counts were made over the lower back. Approximately four and one-half hours after the tracer dose was given

and after the counts seemed to have reached a plateau, he was given 2 grams of potassium thiocyanate. Immediately thereafter there was a rapid fall in the counts over the gland and a rise in the radioactivity over the lower back. After two hours, counts over the thyroid had dropped 70 per cent.

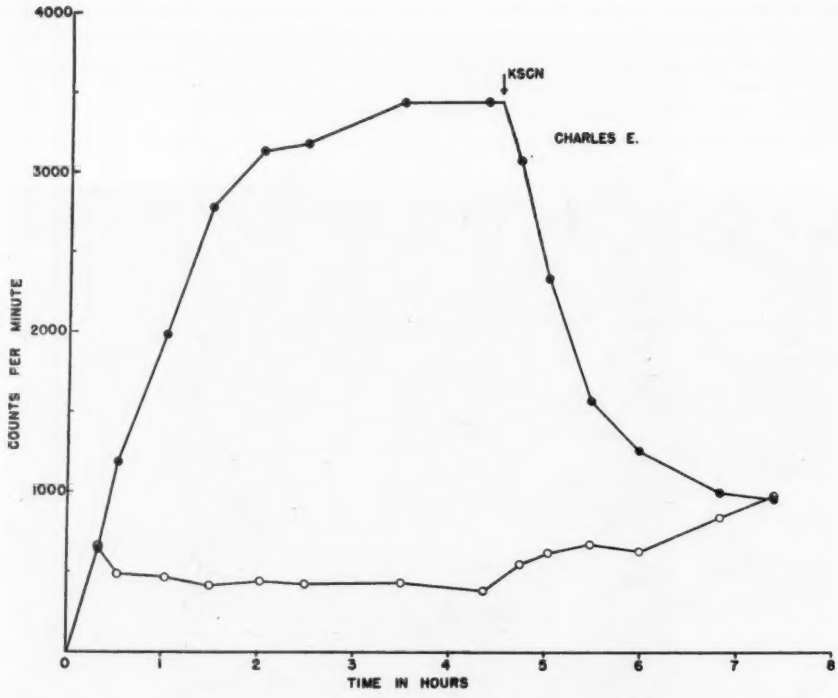

FIG. 6. Radioactive iodine accumulation and discharge in Charles E., Case II. At zero time a tracer dose of 100 microcuries of radioactive iodine was given by mouth. The open circles represent net counts per minute over the lower back; the closed circles represent net counts per minute over the thyroid gland. At the indicated point, the patient received 2 grams of potassium thiocyanate by mouth.

Case III

Robert E., *MGH Unit #357136* (Fig. 7), aged 13 years, was brought to the hospital for study. His mother was confused about his early development, but at an early age a diagnosis of cretinism had been made and he had been started on desiccated thyroid, 1 grain daily. This was continued only sporadically. At the time of admission he had had no thyroid medication for approximately four months. Although development had been slow, he had learned to feed himself, to walk and to engage in simple play. He had never been to school. Bowel and bladder control had been learned.

Physical examination: The pulse was 80, respirations 20 and blood pressure 80 systolic and 60 diastolic. His height was 118 centimeters and his weight 29.4 kilograms.

The hair was straight and slightly coarse. The skin was bronzed, dry, thickened and spongy. The bridge of his nose was depressed. The tongue was normal. The lips were protuberant. The thyroid was enlarged to about three times normal size and there was a faint bruit. Examination of the heart, lungs and abdomen revealed nothing abnormal. The phallus was very short. No testes could be palpated in the scrotum. There was no diastasis recti. He walked with a slightly widened base and with a shuffling gate.

Radioiodine studies: Following a tracer dose of 100 microcuries of radioactive iodine (Fig. 8), the counts over the thyroid gland increased very rapidly. Control observations were made by counting over the thigh. The counts over the thyroid gland declined slowly for the next three hours. Approximately four hours after administration of the

FIG. 7. Case III, Robert E. Cretinism was recognized at an early age, but treatment was sporadic. The thyroid was enlarged to about three times normal size.

radioactive iodine he was given 2 grams of potassium thiocyanate by mouth. This was followed immediately by a rapid discharge of the radioactive iodine from the thyroid. One hour after the thiocyanate was given the counts were approximately 10 per cent of the previous level.

Case IV

Norma E., a 25-year-old sibling of Patients I, II and III, was brought to the laboratory for study only. Except for the usual childhood diseases she had always been entirely well. She has never had symptoms suggestive of diminished thyroidal function. She had

completed the third year of high school and made her living working in a factory. Her only complaint was of moderate obesity. The only developmental detail of interest was that this patient, together with her 2 apparently normal siblings, was given cow's milk during the first few months of life, whereas the 4 goitrous siblings were breast fed. Neither in this patient nor in the rest of the family was there any evidence of ingestion of any recognized goitrogen. It was customary for the family to have fish two or three times each week.

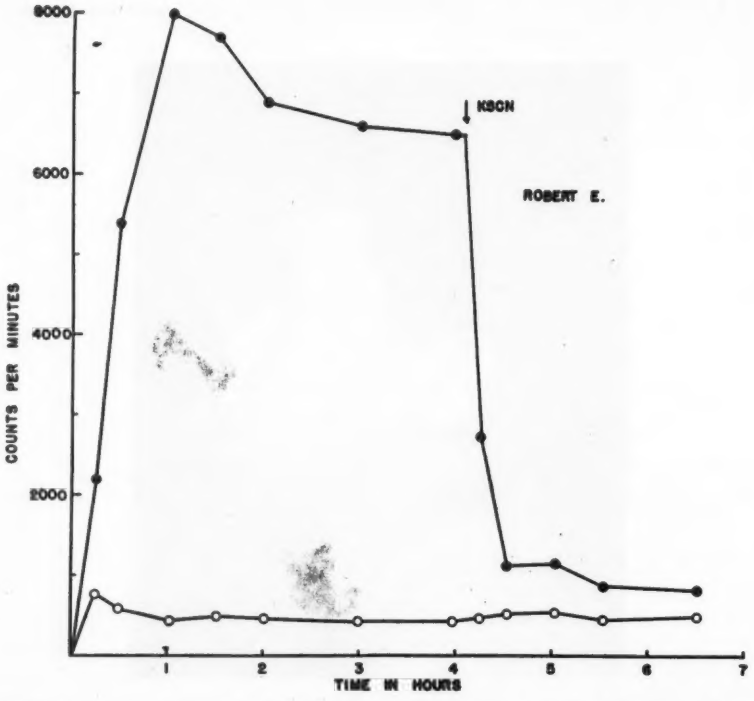

FIG. 8. Case III, Robert E. At zero time, a tracer dose of 100 microcuries of radioactive iodine was given. The open circles are net counts per minute over the thyroid gland; the closed circles are net counts per minute over the thigh. The patient received 2 grams of potassium thiocyanate by mouth at four hours.

Radioiodine studies: She was given a tracer dose of 100 microcuries of radioactive iodine (Fig. 9). This accumulated slowly in the thyroid gland. Approximately twenty-six hours after the radioiodine was administered, and at a time when the counts over the thyroid had reached a plateau she was given 2 grams of potassium thiocyanate by mouth on an empty stomach. There was no appreciable change in the counts during the succeeding three hours.

DISCUSSION

The sporadic goitrous cretin presents a paradox. In spite of an abundance of thyroid tissue and in spite of an adequate dietary supply of iodine there is ample clinical and laboratory evidence of insufficient supply of thyroid hormone to the tissues. The low concentration of protein-bound iodine in the blood is consistent with failure of the gland to release hormone. It

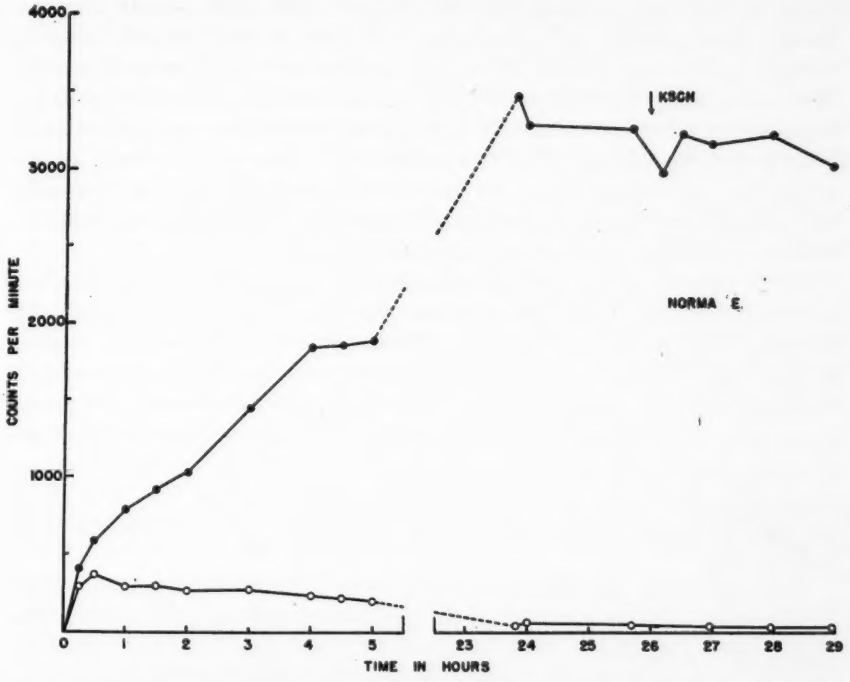

FIG. 9. Radioactive iodine accumulation in Norma E., Case IV. At zero time, a tracer dose of 100 microcuries of radioactive iodine was given. Potassium thiocyanate (2 grams) was given by mouth at the twenty-seventh hour. Closed circles are net counts per minute over the thigh; open circles are net counts per minute over the thyroid gland.

would seem, therefore, that such patients must have a block to one of the steps in synthesis. Hyperplastic enlargement of the gland might be interpreted as a compensatory phenomenon. The thyroid hyperplasia occurring during thiouracil administration comes to mind as an analogous situation.

The production of thyroid hormone proceeds in an orderly fashion from the accumulation of iodide by the gland to the delivery of finished hormone to the blood (5). The inorganic iodide of the serum may be concentrated

as inorganic iodide in the hyperplastic gland of the rat to 250 times the blood concentration (6). This trapped iodide then undergoes oxidation to iodine and is fixed to tyrosine groups, becoming the "diiodotyrosine-like" fraction of Chaikoff (5). These groups are then combined to form the "thyroxin-like" fraction, which is then either extruded into the blood or stored within the follicle as thyroglobulin. Vanderlaan and Vanderlaan (6) found that thiocyanate ion behaves in many respects like iodide. It specifically inhibits the trapping mechanism for iodide. Thiocyanate also discharges iodide which had already been trapped by the thyroid, but it is unable to discharge iodide which has undergone oxidation and become fixed into a protein complex. Thus, by administering a dose of thiocyanate to a patient who has previously been given radioiodine one can estimate what proportion of the radioactive iodine in the thyroid is in the inorganic iodide fraction and what part has been incorporated into protein. Normally this proportion of inorganic iodide in the gland is so small that the administration of thiocyanate causes no detectable change.

In the normal and in the hyperplastic gland a tracer dose of radioiodine accumulates in the thyroid for a period of several hours and only gradually disappears during succeeding days. Patient IV, the sibling who on clinical grounds had a normally functioning thyroid gland, handled her tracer dose of radioiodine in a normal fashion. Counts increased slowly over the gland for at least five hours. The administration of 2 grams of potassium thiocyanate many hours later when the counts were fairly steady caused no noteworthy discharge of radioiodine. One might conclude that this gland was accumulating iodide and binding it into an organic compound at a normal rate.

The radioiodine uptake and discharge curves from the 3 goitrous subjects were in striking contrast to the curve obtained from the normal sibling. They are similar to those obtained by Stanley and Astwood (7) from subjects with hyperplastic glands blocked by mercaptoimidazole or propylthiouracil. In each case the radioactive iodine accumulated in the thyroid gland at an extremely rapid rate, and a plateau was reached in approximately two hours. Following the administration of thiocyanate the radioactivity over the gland diminished with great rapidity and to such a degree that the counts fell 70 to 90 per cent two hours later. The fact that thiocyanate did not release all of the radioactive iodine from the gland suggests that there might have been some conversion of iodide into hormonal iodine. This is by no means certain however. Had all the radioiodine been extruded from the thyroid parenchyma into the blood, an appreciable amount of radioactivity would have been detected over the gland because of the intense vascularity present. Patient II demonstrated a rise in radioactivity over the left lower chest posteriorly, a vascular area, following ad-

ministration of the thiocyanate, presumably because a large amount of radioiodine was added to the blood from the thyroid gland where it was stored. The failure to form an appreciable amount of hormone is confirmed by the very low values of protein-bound iodine in the tissue removed at operation in 2 of these patients and the low values for serum protein-bound iodine in all 3.

From the foregoing, it seems reasonable to assume that the 3 cretinous subjects had no impairment in their ability to extract iodide from the blood. Rather the defect is an inability to incorporate the iodide into tyrosin. There are several possible explanations for this. There may be an absence of the mechanism necessary for the oxidation of iodide to iodine. There may be an abnormal metabolite present which acts in the same way as the thiocarbonamide or aminobenzene groups of drugs. Our data furnish no clue as to what the intimate defect may be.

Stanley and Astwood (7) found that radioactive iodine accumulates in the thyroid gland of thiouracil-treated subjects within the first two hours and then slowly disappears within the next twenty-four hours. If our explanation for the results in these cases is correct, why then was there so little change in the counts registered over the gland in Case I, twenty-four hours after a plateau had been reached? One explanation is that this enormous gland had such a large iodide space compared to blood that relatively little iodide was available for excretion by the kidney.

SUMMARY

Three of 4 goitrous cretins from a single family and 1 normal sibling have been studied with radioactive iodine. The effect of thiocyanate on the accumulation of radioactive iodine has been determined. In contrast to the normal sibling, who accumulated the radioactive iodine in her thyroid gland at a normal rate and who did not discharge it after the administration of thiocyanate, the 3 goitrous cretins accumulated the radioactive iodine rapidly and discharged it immediately after they were given potassium thiocyanate. This is interpreted to mean that the cretinous members of the family were able to extract iodide from the blood, but were unable to convert it into an organically bound form. The result was intense compensatory hyperplasia of the gland which was in turn followed by degeneration and fibrous tissue replacement.

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AN INTERPRETATION OF THE GOITROGENIC PROPERTIES OF CERTAIN "ANTITHYROID" AGENTS*†

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THE discovery of the antithyroid activity of certain drugs furnished a tool and a renewed stimulus for the study of the mechanism of thyroid function. One of these agents, thiouracil, was early recognized as an effective chemotherapeutic agent for the control of thyrotoxicosis. Unfortunately, thiouracil, the most active of these early agents, proved not to be an unmixed blessing since it possesses properties which lead to many undesirable reactions. Despite the study and publication of results on several hundred compounds, no ideal antithyroid agent has been found.

The mechanism of action of the antithyroid agents is not clear. Evidence indicates there is an interference by these agents with the thyroid content of oxidative enzymes. Moreover, it appears that the conversion of iodide to free iodine and thus the conversion of iodide to organic forms is blocked. For example, the formation of diiodotyrosine is depressed. Iodine participates in many vital reactions in the thyroid gland. According to De Robertis (1) it prevents the breakdown of the globulin portion of thyroglobulin by inhibiting proteolytic enzymes of the thyroid. The fixation of iodide in the production of thyroxine is catalyzed by thyroid-stimulating hormone (TSH). Excessive levels of iodide inhibit this and other actions of TSH. Thus the actual formation of active thyroid hormone depends upon the quantitative relationship of iodine to thyrotropin, the rate of activation and inactivation of TSH, the level of oxidase activity in the thyroid, and probably many other unknown factors (2, 3).

For a number of years we have been synthesizing derivatives of thiouracil in the hope of preparing a more effective antithyroid agent. Since large amounts of iodine are known partially to inhibit the antithyroid ac-

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tion of thiouracil, an attempt was made to prepare iodine derivatives of thiouracil. Williams (3), thinking along similar lines, stated that it appeared impossible to obtain such a compound by synthesis, since the necessary introduction of a protective substituent attached to the sulfur atom would result in loss of antithyroid activity. Nevertheless, Barrett *et al.* (4), successfully synthesized 5-halogeno-2-thiouracils, among them 5-iodo-2-thiouracil. Despite the great difficulties, synthesis was pushed to successful completion in hopes of providing a potent antithyroid agent, the action of which would be tempered by the alleviating features of iodine. It was expected also that, because of the great affinity of the thyroid for iodine, a greater concentration of the iodinated drug in the thyroid could result. This would permit the use of smaller and consequently less toxic amounts of the agent. Furthermore, it was thought that the iodine substitution might produce a qualitative or quantitative change in the behavior of the parent compound in the thyroid while simultaneously increasing the iodine concentration in that gland. In other words, it seemed worthwhile to study the effect of such a compound on the thyroid gland which has been offered additional iodine with the drug that interferes at the same time with the gland's mechanism of iodine utilization. Lastly, in view of the ability of free iodine to inhibit thyrotropin in the gland, thyrotropin would be progressively inhibited and the hyperplasia usually accompanying thiouracil treatment would be lessened.

EXPERIMENTAL

To evaluate the potency of "antithyroid" drugs in experimental animals, we have employed two groups of criteria: a) those concerning the goitrogenic action, and b) those pertaining to the antithyroid action, as shown in Table 1.

Goitrogenic action is almost entirely the result of active TSH which may be either increased in amount or augmented in potency. Antithyroid action is depicted in the involution of a hyperplastic gland or a structural depression of the normal thyroid with loss of iodine and blocking of iodine uptake. The effect of the animal's own pituitary TSH and that supplied from exogenous sources is minimized or abolished and consequently the basal metabolic rate is lowered. 5-Iodo-2-thiouracil was evaluated according to these criteria and compared to other halogenated thiouracil derivatives.

Oxygen consumption. All halogenated thiouracils lowered the oxygen consumption of the rat; 5-iodo-2-thiouracil produced a depression of 20 per cent, as did thiouracil and thiouracil plus KI. The rats received 39 micromols/100 Gm. initial weight in drinking water daily for twenty-seven days. The dosage was doubled for twenty-one days, the remaining period

of therapy. During the recovery period the significant finding was the prolonged depression shown by animals formerly treated with the 5-iodo derivative. In the other groups receiving thiouracil with and without KI, or the bromo and the chloro derivatives, the oxygen consumption returned

TABLE 1. CRITERIA FOR EVALUATION OF "ANTITHYROID" AGENTS

Goitrogenic action	Criterion	Antithyroid action
↑	Thyroid weight	↓
↑	Thyroid hyperplasia	↓
↑	Thyroid vascularization	↓
↑	Thyroid cell height	↓
↓	Thyroid colloid in follicles	↑ →
↑	Thyroid colloid droplets in cells	↓
↓	Iodine content	↓
↓	Iodine uptake	↓
↓	TSH-pituitary	↑ →
↑	TSH-circulating	↓
↑	TSH-in vitro	↓
↓	Basal metabolic rate	↓

to normal within four to eight days after the drug was withdrawn; but in the 5-iodo-treated animals it remained lower than in the controls for eighteen days. A detailed account of this phase of the work is in preparation for publication (5).

Two of the iodinated derivatives prepared for this study by the Ciba

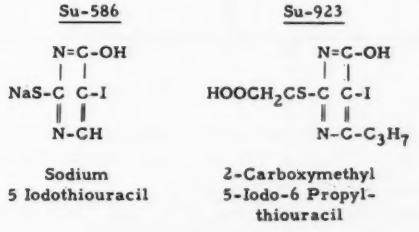

FIGURE 1

Research Laboratories, according to the method of Barrett (4), are illustrated in Figure 1. These compounds henceforth will be referred to as 5-iodo-2-thiouracil and Su-923.

The Ciba Research Laboratories made similar studies on oxygen consumption with 5-iodo-2-thiouracil (Su-586). In addition, Su-923 was tested

and found to be even more effective in lowering the oxygen consumption. The rate of oxygen consumption dropped steadily, and it reached 25 per cent below the normal level at the ninth week (Fig. 2).

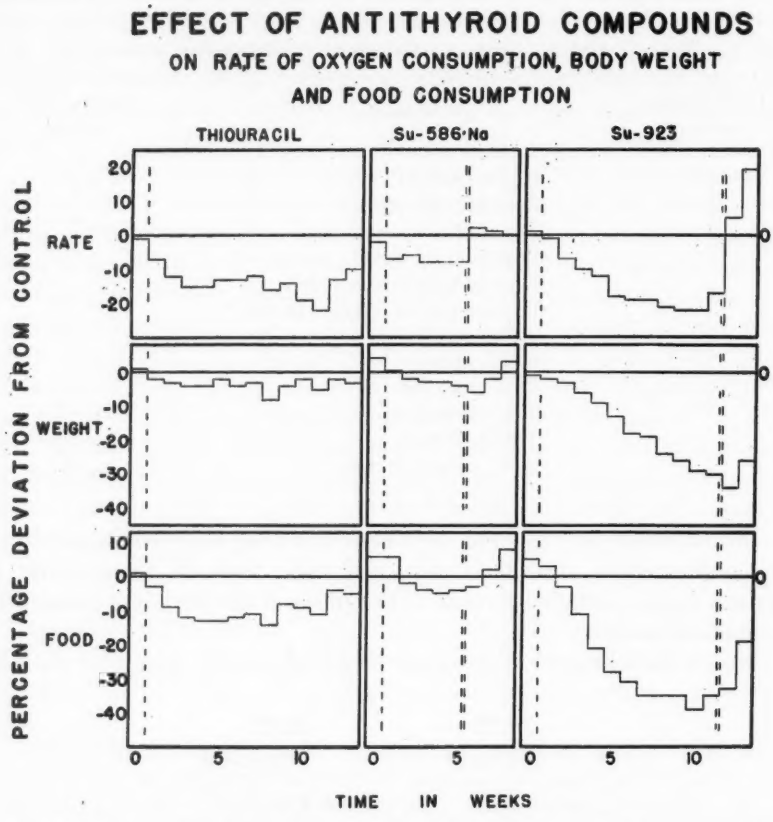

FIG. 2. Top row: Basal metabolic rate is measured by the Haldane open-circuit method. (Haldane, J. S.; *J. Physiol.* **13:** 419, 1892, modified by Jay Tepperman, Syracuse University Medical School, unpublished.)

All groups, including control, consisted of 10 rats. Thiouracil was administered for the duration of the experiment. Su-586 administration was discontinued at the end of the fifth week. Su-923 was continued until the end of the eleventh week. Animals were sacrificed at the time indicated in the last week for weighing and for histologic studies of thyroid gland and other organs. The drugs were administered mixed with the food in molar quantities equivalent to 0.1 per cent thiouracil.

Iodine uptake. Dr. William Money of the Sloan-Kettering Institute for Cancer Research completed a trial with 5-iodo-2-thiouracil determining

the radioactive iodine uptake. He treated chicks for three days with TSH and injected the iodothiouracil on the fourth day; then gave 2 microcuries of I^{131} one hour later. He found that the 5-iodo derivative effectively blocked the uptake of I^{131}, even moreso than did thiouracil or propyl thiouracil.

TABLE 2. UPTAKE OF I^{131} BY CHICK'S THYROID TREATED WITH 5-IODO-THIOURACIL, THIOURACIL AND PROPYL THIOURACIL

	Thyroid weight, mg.	Uptake of I^{131}, % per gland	Uptake of I^{131}, % per mg. thyroid	Uptake of I^{131} by controls, % per gland
5-Iodo-2-thiouracil (mg.)				
12 animals in each group				
0	11.4	23.3	2.10	
0.5	12.1	14.2	1.63	60.0
1.0	11.4	2.52	0.22	10.8
5.0	10.6	0.218	0.021	0.94
10.0	11.7	0.014	0.004	0.06
25.0	12.3	0.036	0.003	0.15
*Thiouracil (mg.)**				
10–20 animals in each group				
0		44.0		
0.1		29.7		67.5
0.5		21.2		48.2
1.0		25.4		57.5
5.0		1.4		3.2
10.0		1.2		2.7
*Propyl thiouracil (mg.)***				
10-20 animals in each group				
0		14.0		
0.1		7.4		53.1
0.5		4.9		35.4
1.0		3.9		27.9
5.0		1.0		7.1
10.0		0.3		2.3

* From Larsen, Keating, Peacock and Rawson (11).

** From McGinty, Rawson, Fluharty, Wilson, Riddell and Yee (12).

The results of one experiment are shown in Table 2. Williams (6) in 1947 observed a similar antagonism to the uptake of radioactive iodine in the rat after oral administration of the 5-iodo compound.

Urinary excretion. One of us (A.J.P. (7)) conducted a study of the urinary excretion of iodothiouracil in a dog receiving 200 mg. of the drug intravenously and dogs receiving a single dose of 400 and 600 mg., respect-

ively, by the oral route (tube feeding). In all instances the urine was collected for twenty-four hours. The chromatographic method used for the determination has been described previously (8). Table 3 summarizes the results. It will be seen that after intravenous administration, 11 per cent of the compound could be accounted for, with 3.6 per cent appearing as noniodinated thiouracil. Neither 5-iodo-thiouracil nor thiouracil was found after eight hours following intravenous administration. The total excretion

TABLE 3. URINARY EXCRETION OF SODIUM 5-IODO-2-THIOURACIL (SU-586) BY THE DOG*

	0–1 hr.	*1–2 hrs.*	*2–4 hrs.*	*4–6 hrs.*	*6–8 hrs.*	*8–24 hrs.*	*Total excretion*	
				Dog No. 1—Weight 8.8 Kg.—Dose 200 mg. I.V.				
Su-586	1.4	1.1	3.1	6.9	2.4	—	14.9 mg.	7.45%
2-Thiouracil	—	0.3	1.1	2.0	—	—	3.4 mg.	
Su-586 split**							7.3 mg.	3.65%
								11.10%
				Dog No. 2—Weight 9.0 Kg.—Dose 400 mg. orally				
Su-586	0.3	0.6	9.5	19.1	0.3		29.8 mg.	7.45%
2-Thiouracil	0.5	0.4	2.8	5.8	5.3		14.8 mg.	
Su-586 split**							31.8 mg.	7.95%
								15.40%
				Dog No. 3—Weight 8.9 Kg.—Dose 600 mg. orally				
Su-586	2.2	10.6	17.1	13.8	1.4	1.7	46.8 mg.	7.80%
2-Thiouracil	0.3	1.4	4.3	3.5	6.4	10.6	26.5 mg.	
Su-586 split**							54.8 mg.	9.13%
								16.93%

* Dogs were fasted overnight before drug administration. Specimens were obtained by catheterization, except for overnight specimens, which were collected in a metabolism cage.

** Each mg. of thiouracil excreted represents the splitting of 2.15 mg. of sodium 5-iodo-2-thiouracil.

was slightly higher (15.4–16.9 per cent) after the oral administration of the larger doses, with approximately one half of the amount demonstrable as iodine-free thiouracil. Where the split of the iodo-thiouracil occurs, whether the same ratio of split and nonsplit compound holds also in the blood or in the thyroid gland, and what happens to the amount presently unaccounted for, can be decided only by further studies which are under way. These may throw some light on the complex structural and functional changes of the thyroid as here reported.

Goitrogenic properties. The goitrogenic effect of thiouracil, 6-propyl

thiouracil with and without KI, and of the 5-iodo-2-thiouracil as well as of 6-iodo-6-propyl thiouracil was determined by feeding chicks for three weeks. The drugs were added to the diet in amounts equimolar to 0.1 per cent 2-thiouracil. It is apparent from Figure 3 that thiouracil alone produced the largest glands. The thyroids of chicks fed 2-thiouracil and KI

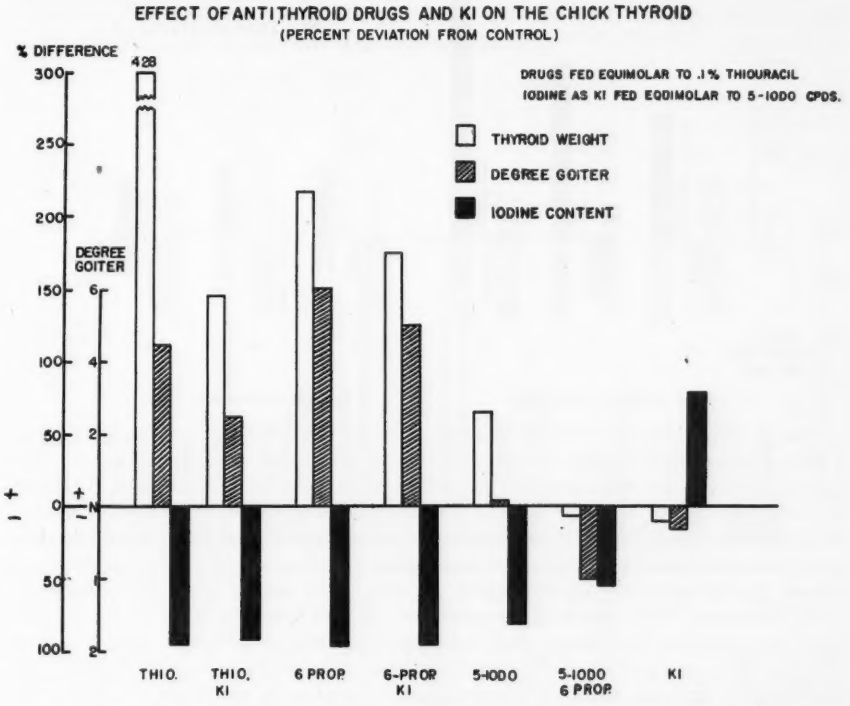

FIG. 3. The effect of thiouracil, thouracil plus KI, 6-propyl thiouracil, 6-propyl thiouracil plus KI, 5-iodo-2-thiouracil, 2-carboxy-5-iodo-6-propyl thiouracil (Su-923) and KI on the thyroid weight. The structural changes (degree of goiter) and iodine content of the gland are plotted in per cent difference from the normal control group observed under the same conditions and at the same time. (For the evaluation of the "degree of goiter" *see* footnote 1.)

were only one third as large as the glands obtained with 2-thiouracil. 6-Propyl thiouracil produced smaller glands which were one half as heavy as those obtained with 2-thiouracil. The addition of KI had but slight effect on this value. 5-Iodo-2-thiouracil increased the thyroid weight only by 60 per cent. In sharp contrast, compound Su-923 produced a slight decrease in thyroid weight. It was interesting to note that, histologically, 6-propyl thiouracil produced the most severe hyperplasia in spite of the fact that the glands

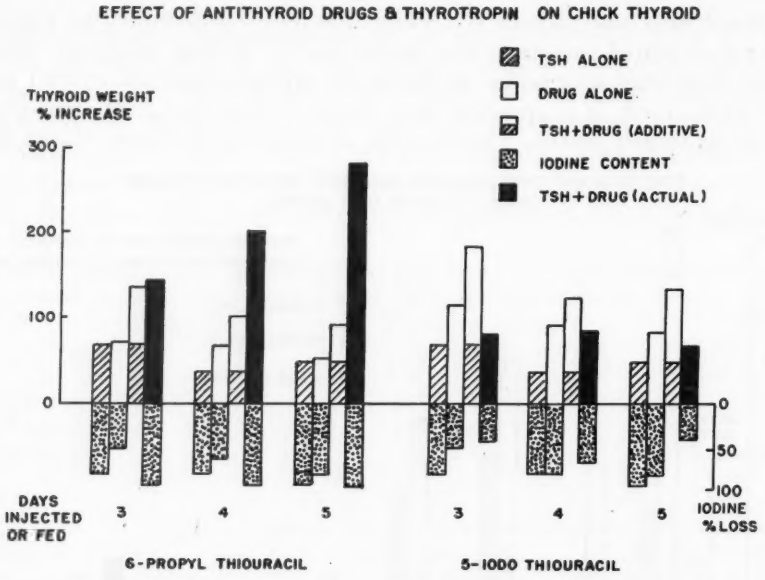

FIG. 4. Thyroid size and iodine content of chicks treated with thyrotropic hormone (TSH) and 6-propyl thiouracil or 5-iodo-2-thiouracil for three, four, and five days. The thiouracil derivatives were mixed with the food at 0.1 per cent concentration. TSH was injected daily so that the total amount given during the experimental periods amounted to .5 unit per chick. Twenty-four hours after the last injection, the animals (12 in each group) were sacrificed along with a corresponding control group. The cross-hatched bars denote the change of the thyroid size in per cent of the control group after treatment with TSH alone. The open bars represent the effect of the drug alone. The solid bars show the actual per cent change after combined treatment of TSH and drug. The bars between the open and the solid bars (combined cross-hatch and open) indicate the theoretically expected effect of the combination treatment, assuming the effect was a plain additive one. The iodine loss is shown also as per cent difference from the untreated controls by the bars extending below the zero line. No theoretic value has been entered for iodine loss for obvious reasons.

weighed less in comparison to the thiouracil-treated ones. KI reduced the degree of goiter[1] in a manner parallel to the weights. 5-Iodo-2-thiouracil glands were essentially normal, the increased weight being due to enlarged

[1] The "degree of goiter" was evaluated by the method of Gassner (9) which is based on a standard using criteria such as follicle size and shape; cell height, shape and number; colloid content, density, and staining affinity (modified Mallory's); vascularity and stromal variations, etc. This standard classifies 10 groups of glands, each being assigned a mathematical score ranging from +1 to +6 denoting increasing degree of goiter, and −1 to −4 indicating diminishing activity when compared with normal control glands which are rated as 0. A similar method has been employed by Astwood (10).

follicles and not to hyperplasia. The iodinated propyl thiouracil produced hypoplastic glands which were rated as minus 1. KI caused a slight hypoplasia of the glands as expected.

The loss in thyroid iodine was almost maximal with thiouracil and propyl thiouracil and only slightly less when iodine was given with thiouracil. 5-Iodo-2-thiouracil caused a surprisingly great loss in iodine, whereas the iodinated propyl compound was less effective.

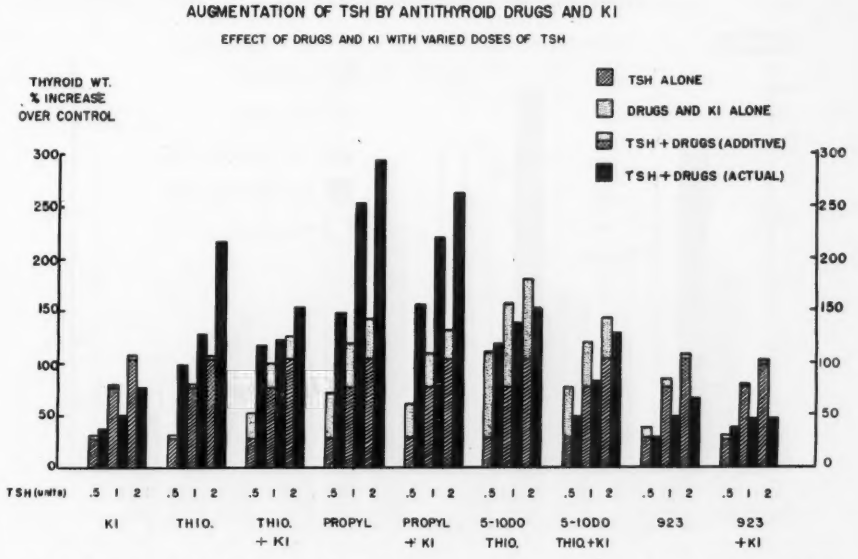

FIG. 5. Effect of TSH given daily at 3 total dose levels (0.5, 1.0, 2.0 units) for five days, alone and simultaneously with thiouracil (=thio.), propyl thiouracil (=propyl), 5-iodo-2-thiouracil (=5-iodo), 2 carboxymethyl-5-iodo-6-propyl thiouracil (=923), with and without KI. The thiouracil compounds were mixed with the food in concentrations equimolar to 0.1 per cent thiouracil. The KI quantities corresponded on an equimolar basis to the iodine content of 5-iodo-2-thiouracil. All animals, with their corresponding control groups, were sacrificed twenty-four hours after the last injection. All bars indicate per cent of thyroid weight increase over control. Cross-hatched bars represent the effect of TSH alone, stippled bars on top of cross-hatched bars the effect of the drug alone, or KI alone and with drugs. Both these bars imply the theoretically expected value if the effects were merely additive. The solid bars show the effect of the combined treatment of TSH and drug, or TSH, drug and KI.

Figure 4 shows the effects on the chick thyroid when antithyroid drugs were fed at 0.1 per cent concentration and thyrotropin[2] was injected. The

[2] Total dose, 0.5 units for three, four or five days of thyrotropin preparation Rx-099802, containing 6 to 8 units (Junkman-Schoeller) per mg. of powder, according to the assay by Dr. R. W. Rawson. Supplied by Parke, Davis and Company.

agents were administered for three, four, or five days. It is striking how the augmentary effect of 6-propyl thiouracil on TSH is stepped up during the fourth and fifth day and equally striking is the lack of such effect on TSH shown by 5-iodo-2-thiouracil. The loss of thyroid iodine after 5-iodo-2-thiouracil is almost the same as with propyl thiouracil. Differences become

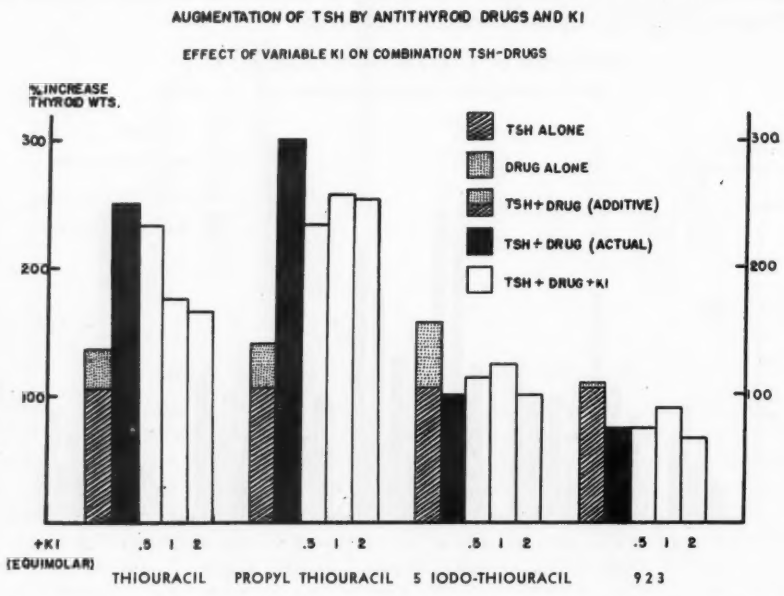

FIG. 6. Influence of KI in varying doses on the effect of TSH and thiouracil derivatives, both alone and combined, on the thyroid weight of the chick. KI was given in amounts $\frac{1}{2}$, 1 and 2 equimolar to the iodine present in the iodinated thiouracils. The experiment was designed and the graph treated in the same fashion as shown in Figure 5.

manifest, however, and the loss in iodine is less pronounced when TSH and iodothiouracil are administered simultaneously.

Figure 5 shows the effect of variable doses of TSH with constant doses of drugs and KI and combinations thereof on the chick thyroid.

Again the augmentative potency of thiouracil and especially of propyl thiouracil compared with TSH alone becomes manifest. This effect is considerably reduced by the addition of KI in the case of thiouracil but remains high with propyl thiouracil and KI. 5-Iodo-2-thiouracil again fails to augment TSH; in fact, the effect seems slightly inhibitory and even more so when KI is added. At all levels TSH potency is greatly reduced when

given with the iodinated compound 923 and strikingly so when iodine is added to this combination.

Figure 6 summarizes the effects of variable doses of iodine as KI given with constant doses of TSH and thiouracils, and combinations thereof. Augmentation of TSH by the thiouracils is shown again, as is the lack of augmentation by the iodinated thiouracil. The addition of iodine as KI effectively counteracts the augmentative potency of thiouracil and less so of propyl thiouracil. The iodinated thiouracils are little affected.

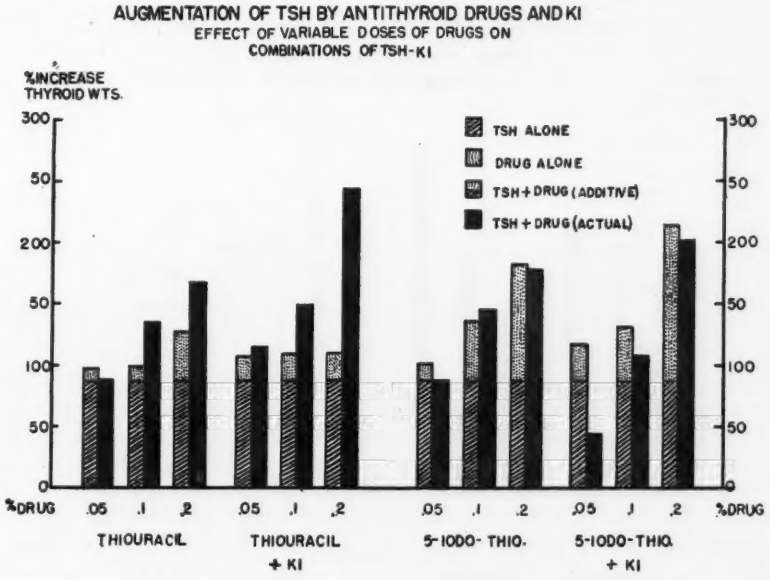

FIG. 7. Thyroid weight of chicks as affected by various dose levels of thiouracil and iodo-thiouracil while under treatment with a constant dose of TSH (1 unit) with and without addition of KI in quantities equimolar to iodine in iodo-thiouracil. Experiment and graph were designed in the manner shown in Figure 5. The two drugs were mixed with the food in concentrations as indicated above, always equimolar to thiouracil.

Figures 7 and 8 show the percentage increase in thyroid weights obtained when a constant dosage of TSH and KI is given with .05, 0.1, and 0.2 per cent levels of 2-thiouracil and equimolar amounts of the related drugs.

With increased concentrations of thiouracil or propyl thiouracil alone, little additional increment in the thyroid weights was noted except with the highest dose. When TSH was added, a striking increase in gland weights was evident. The addition of iodine as KI caused a further increase in thyroid weights showing a stronger augmentation of TSH. In Figure 8 a tre-

mendous augmentative power of the propyl thiouracil is manifested. At the lower doses of propyl thiouracil, KI slightly diminished this augmentation, whereas at the highest dose level the augmentation was even more pronounced than in the case of thiouracil.

In contrast to the markedly increased thyroid weights obtained after administration of combined TSH-thiouracil, or more so after TSH-propyl thiouracil treatments, the iodinated thiouracil combined with TSH produced a thyroid not larger than could be expected. As a matter of fact,

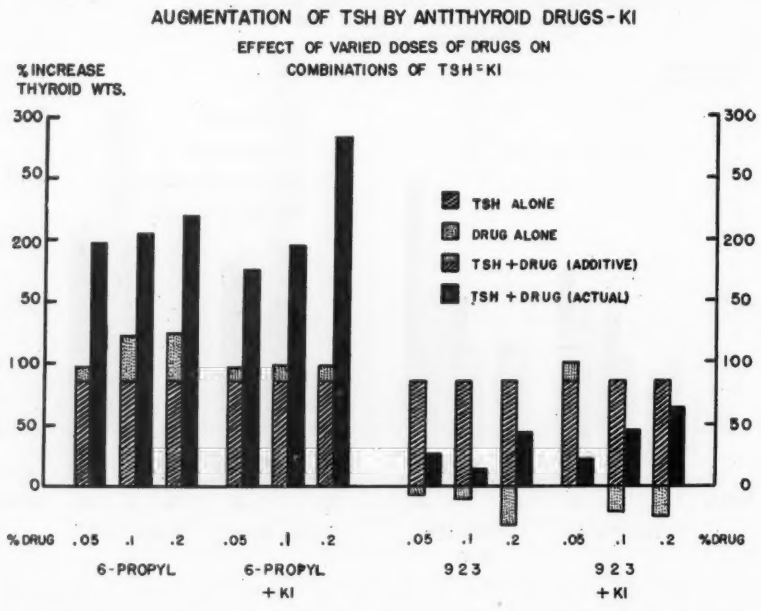

FIG. 8. Same as Figure 7, using propyl thiouracil and carboxymethyl-5-iodo-6-propyl thiouracil (923).

with the lowest dose of iodothiouracil plus KI, the thyroid remained smaller than with the same dose of TSH when given alone. This is still more pronounced in case of treatment with compound 923, in which case a loss of TSH activity was noted at all dose levels. The small loss in thyroid weights when 923 was given alone or with KI remains unexplainable. This is somewhat in contrast to the results from corresponding experiments illustrated in Figures 5 and 6 (the bars on the right side). The addition of KI to 923 changes the behavior of the gland but little after treatment with this drug.

DISCUSSION

The findings reported with the chick thyroid as test object, supported by the excretion studies in the dog and the iodine-uptake studies using the chick thyroid, demonstrate that the effect of iodinated thiouracils is both quantitatively and qualitatively different from that of noniodinated thiouracils. It is also evident, in spite of the demonstration that part of the iodo-thiouracil appears in the urine in the form of noniodinated thiouracil, that the addition of inorganic iodide (KI) to thiouracil does not imitate the effect of iodo-thiouracil. In this respect it should be emphasized that TSH combined with thiouracil or propyl thiouracil always produces a larger thyroid than does TSH alone or the antithyroid drug given alone; and furthermore, that this combination produces larger glands than would be expected from a simple additive effect of TSH plus the drug. This augmenting effect is not produced by a combination of TSH with iodo-thiouracil or compound 923. It should be kept in mind that KI added to the iodinated drug fails to change this situation. An explanation for all these findings is not offered at this time. However, in the light of the presented results and those reported elsewhere (5, 6), and since the effect of the iodinated compounds cannot be imitated by adding inorganic iodide to a thiouracil regimen, we may assume that the mechanism of action of iodinated thiouracil must be different from that of noniodinated thiouracil or derivatives thereof. Our results suggest that thiouracil in some way supports, increases, or synergizes the effect of TSH, whereas the iodinated compounds cause an inhibition of TSH. We are using this as a working hypothesis until further conclusive proof becomes available.

SUMMARY

Data are presented which indicate that, in the animals tested, 5-iodo-2-thiouracil is a potent antithyroid agent but possesses little if any goitrogenicity when compared with noniodinated thiouracil.

Acknowledgments

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TWO CASES OF ALBRIGHT'S SYNDROME OBSERVED IN BRAZIL

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ALBRIGHT (1, 2) stated: "A case with precocity and cutaneous pigmentation but without evidence of bone lesions such as that described by Kurzrok could be designated *polyostotic fibrous dysplasia sine fibrous dysplasia.*"

The author has observed in Brazil 2 cases which seemed to fit exactly into this incomplete form of the syndrome; however, a second and more detailed x-ray examination revealed some very discrete bone lesions.

CASE REPORTS

Case 1. F. W. was a white female, born December 12, 1948. She was 15 months old on the day of the examination, and at that time had not had any of the common diseases of childhood.

During pregnancy, her mother had a serious anemia, for the treatment of which she received two blood transfusions. From infancy this woman had a slightly raised, chocolate-colored round spot, 3 inches in diameter, on the lumbar region. She also showed another brown spot, which was oval but somewhat irregular in shape, was not raised, and extended from the lateral aspect of the abdomen on the right to the lumbar region, its lower fringe touching the apex of the iliac bone. She had also been operated on, in 1946, for "ovarian cyst."

The patient was born prematurely at seven and a half months of pregnancy and she had neither toenails, nor fingernails.

At the age of 2 months she sat for the first time; the first tooth appeared at 8 months of age and she walked at 14 months.

Three weeks after her birth the spots shown in Figures 1, 2 and 3 were detected. On May 1, 1949 (when 5 months old) the baby showed a chocolate-colored vaginal discharge, which lasted for five days. At the beginning of August (when 8 months old) she had another vaginal discharge, this time discontinuously and of darkish blood, which lasted for three days. On November 5, 1949, for a third time the discharge occurred, when the baby was 11 months old; the nurse stated that it was a "perfect miniature catamenial discharge." This lasted for two days and one night. The fourth time (by the end of March, 1950) the baby presented a yellowish-white discharge which lasted only one day and was not abundant enough to soil the clothes. On April 9, 1950, she menstruated again. This discharge lasted for two and a half days, and the diapers had to be changed every two hours.

The baby has a normal appearance, was slightly nervous, and looked brighter than

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FIG. 2. *Case 1.* Pigmentation on the anterior lateral part of the neck.

FIG. 1. *Case 1.* Extensive cutaneous chocolate-colored pigmentation.

one would expect at her age. The whites of her eyes were slightly blue. The vulva was slightly larger than normal.

Anthropometry. Weight, 11.5 Kg.; height, 84 cm. (the normal height for this age in Brazil is 74 cm.); bisacromial measurement, 18.5 cm.; bitrochanteric, 15 cm.; bisiliac, 12 cm.; furcula-xiphoid, 8.0 cm.; xiphoid-pubis, 18.0 cm.; length of arm, 21.5 cm.;

FIG. 3. *Case 1.* Genitalia. Observe the pigmentation extending to the anal margin.

length of forearm, 10.5 cm.; length of leg, 14.3 cm.; antero-posterior thoracic diameter, 11.5 cm.; transverse thoracic diameter, 15 cm.

Laboratory findings. Urinary 17-ketosteroids, 0.4 mg. per twenty-four hours (measured as androsterone); gonadotropins, less than 70 m.u.u. (mouse uterine weight units) per twenty-four hours (on account of the small quantity of urine it was impossible to measure lower levels of excretion); estrogens, less than 10 I.U.

Serum calcium, 10.9 mg. per 100 cc.; phosphorus, 7.2 mg. per 100 cc.; phosphatase, 14 Bodansky units; potassium, 17.6 mg. per 100 cc.; sodium, 321 mg. per 100 cc.; cholesterol, 250 mg. per 100 cc.

Erythrocyte count 4,640,000 per cu.mm.; hemoglobin, 11.5 Gm. (76 per cent); volume of packed red blood cells, 41 per cent; mean corpuscular volume, 89 cubic micra; mean corpuscular hemoglobin, 25 micromicrograms; mean corpuscular hemoglobin concentration, 28 per cent; platelets, 380,000.

Leukocyte count, 5,800; eosinophils, 6 per cent; basophils, 0; myelocytes, 0; metamyelocytes, 0; stab, 1; segmented neutrophils, 24; lymphocytes, 53; monocytes 16 per cent.

Thus, the blood picture of this 15-month-old girl showed a slight macrocytosis an eosinophilia, a monocytosis, and a lymphocytosis.

FIG. 4. *Case 1.* Note the characteristic hyperostosis at the base of the skull, effacement of the sphenoid sinus, and a slightly prominent occiput.

The child's mother, as already stated, presented at the beginning of the pregnancy a severe anemia, and the blood taken in the third month (July 20, 1948) in Lausanne, Switzerland, showed the following values: erythrocytes, 2,780,000; hemoglobin, 60 per cent; color index, 1.1; leukocytes, 7,500; eosinophils, 0 per cent; basophils, 1; myelocytes, 2; metamyelocytes, 0; stab, 18; segmented, 59; lymphocytes, 16; monocytes, 3; and plasmocytes, 1 per cent. As may be seen, the anemia was macrocytic and the white cells showed a neutrophilia without leukocytosis, but with a "shift to the left;" there were also "toxic" granulations in the neutrophils. On October 20, this time in Brazil, the blood picture showed the following results: erythrocytes, 3,500,000; hemoglobin 11 Gm. (75 per cent); volume of packed red blood cells, 33 per cent; mean

corpuscular volume, 94 cubic micra; mean corpuscular hemoglobin, 31 micromicrograms; mean corpuscular hemoglobin concentration, 33 per cent; leukocytes, 8,600; eosinophils, 1 per cent; basophils, 0; myelocytes, 0; metamyelocytes, 0; stab, 45; segmented, 72; lymphocytes, 15; and monocytes 8 per cent. The blood picture had been changed to that of a typical pregnancy anemia, with a slight macrocytic tendency.

FIG. 5. *Case 1.* Left radius and cubitus, showing discrete fibrous appearance at the distal end.

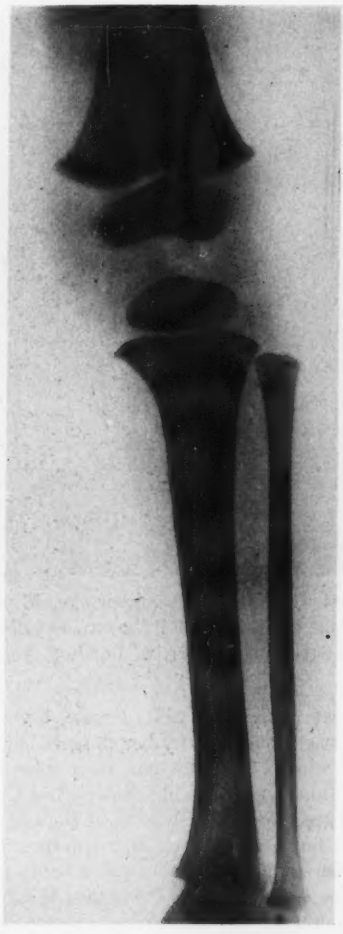

FIG. 6. *Case 1.* Upper third of the tibia, showing increase of density, and bands of calcium density in all extremities of the diaphyses, with marked irregularity of the outline.

X-ray examination (by Dr. R. Duque Estrada). On December 7, 1949, when the patient was 11 months old, the base of the skull showed a marked increase in density, hyperostosis, effacement of the sphenoid sinus, and a slightly prominent occiput. The left radius and cubitus were fibrous. The upper third of the tibia showed an increase in density and there were bands of calcium density in all extremities of the diaphyses, with marked irregularity of the outline. Bone age: 3 years (36 months). Present were

the capitatum (1 year); the uncinatum (1 year); the pyramidale (2 years); and the phalanges and metacarpal bones (3 years). Missing were the semilunar bones (4 years).

On March 30, 1950, when the patient was 15 months old, the semilunar bones were already outlined, the left one more distinct and larger. The bone age was 4 years (48 months). The roentgenograms are shown in Figures 4, 5, 6 and 7.

FIG. 7. *Case 1.* Chronologic age, 15 months; bone age, 3 years (36 months). Present are the capitatum and the uncinatum (1 year); the pyramidale (2 years); and the phalanges and metacarpal bones (3 years). Missing is the semilunar (4 years).

Case 2. H. C., a white female, 5 years and 10 months old, was born May 4, 1944. She was brought in by her parents because she had already menstruated three times; first, when 14 months old, then when 5 years and 7 months old, and lastly when 5 years and 8 months old. The two last times she presented swelling of the breasts, which persisted (Fig. 8). Also once, at the age of $4\frac{1}{2}$ years her breasts swelled for about fifteen days, but there was no menstruation.

She was born at term (with a caul), following a normal pregnancy and labor; she sat for the first time when 7 months old, had her first teeth when 8 months old, and already at that age could say "papai" and "mamãe" (mummy and daddy). Speech and intellect developed very quickly. She walked when 18 months old. Whooping cough started at the age of 9 months, and twice she remained for several hours in a stage of torpor, during the six-month course of the disease.

At the age of 17 months she had severe diphtheria, during which she fell into a state of torpor. After this disease she suffered muscular atrophy of the right leg, which, however, was rapidly regressive.

When 4 years old she had the measles. After this illness, this girl who had previously

had bladder control, became incontinent of urine and had frequency. This condition persisted for about six months.

Her second teeth began to appear when she was 5½ years old. The inferior incisors were serrulated.

When she was 8 days old spots appeared on her skin, which were pink at first; later they became chocolate-colored, which they are at present. These spots (Fig. 9) covered

FIG. 8. *Case 2.* Observe the tumescence of the breasts.

FIG. 9. *Case 2.* (*left*) Cutaneous pigmentation on the right back and left buttock.

FIG. 10. *Case 2.* (*right*) Normal general appearance; no pain, lameness, or fractures.

the interscapular space on the right side, extending under the spine of the scapula; they were not homogeneous, but of the "coast-of-Maine" type. On the left side there was another darker spot, covering part of the buttock and the internatal cleft. There was also a smaller spot (about 1 in.) over the coccyx, and another (1½ to 2 in.), much lighter, over the right buttock.

FIG. 12. *Case 2.* Absence of the olecranon (9 years); outline of the trochlea (9 years).

FIG. 11. *Case 2.* Chronologic age, 5 years and 10 months; bone age, 9 years. All wrist bones were present, with the exception of the pisiform. (In the foot, the tuberosity of the calcaneum was present (8 years).)

It is interesting that this girl's mother has on her arm a spot about 1½ to 2 inches in diameter, of a lighter color, but of the same appearance. The mother first menstruated when 10 years old, and the grandmother when 10½ years old. The father and four other brothers are normal.

The appearance of the girl was normal (Fig. 10), but her attitude and intelligence were those of a older child. She was very sensitive and shy, making it very difficult to examine her genital organs. Her vulva was slightly tumescent and of a violet tinge. The breasts were tumescent and there was no pubic hair. The sclerae were bluish.

Anthropometry. Weight, 21.8 Kg.; height, 114.7 cm. (normal in Brazil for this age, 106); bisacromial measurement, 19.3 cm.; bitrochanteric, 14.7 cm.; bisiliac, 12.6 cm.; furcula-xiphoid, 5.4 cm.; xiphoid-pubic, 19.0 cm.; length of the arm (acromion-olecranon), 17.2 cm.; length of the forearm (olecranon-articular interline of the wrist), 12.9 cm.; length of the thigh (trochanter-articular interline of the knee), 21.5 cm.; length of the leg (articular interline of the knee—external malleolus), 21.8 cm.; antero-posterior thoracic diameter, 9.4 cm.; transverse thoracic diameter, 14.1 cm.

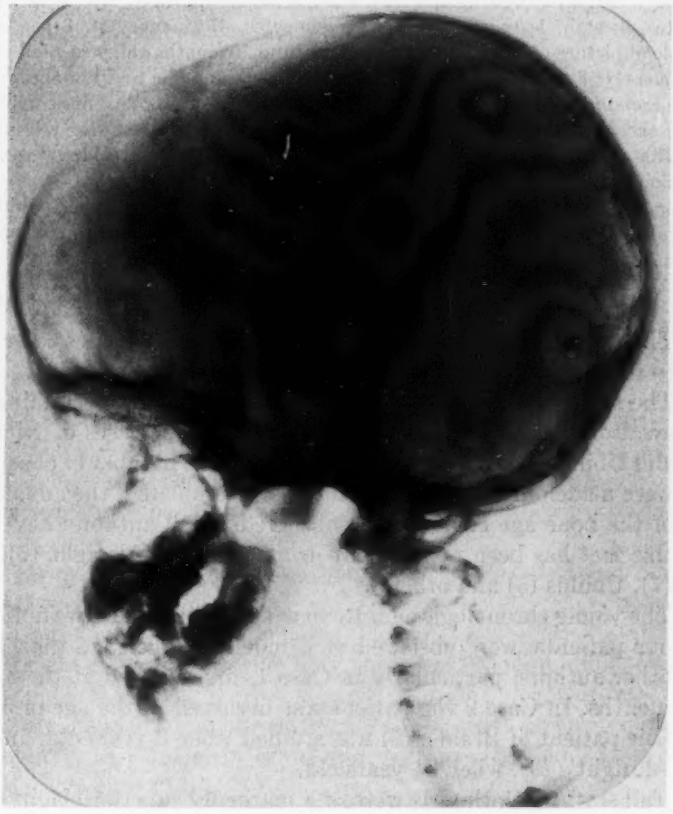

FIG. 13. *Case 2.* A slight increase of density in the anterior and middle cranial fossae; effacement of the sphenoid sinus.

Laboratory findings. Urinary 17-ketosteroids, 4 mg. per twenty-four hours (measured as androsterone); estrogens, 30 I.U.; gonadotropins, less than 10 m.u.u. (mouse uterine weight units).

Serum calcium, 10.5 mg. per 100 cc.; phosphorus, 5.8 mg. per 100 cc.; phosphatase, 13.4 Bodansky units; potassium, 21.4 mg. per 100 cc.; sodium, 298 mg. per 100 cc.; cholesterol, 255 mg. per 100 cc.

Erythrocyte count, 3,640,000 per cu.mm.; hemoglobin, 12 Gm. (80 per cent); volume of packed red blood cells, 34 per cent; mean corpuscular volume, 94 cubic micra; mean corpuscular hemoglobin, 33 micromicrograms; mean corpuscular hemoglobin concentration, 37 per cent; platelets, 310,000.

Leukocyte count, 10,000; eosinophils, 9 per cent; basophils, 0; myelocytes, 0; metamyelocytes, 0; stab, 1; segmented, 35; lymphocytes, 47; monocytes, 8 per cent.

The blood picture of this girl who was 5 years and 10 months old, presented an anemia with a macrocytic tendency, a slight leukocytosis, eosinophilia and lymphocytosis.

X-ray examination (by Dr. R. Duque Estrada). In the wrists all bones were present with the exception of the pisiform. The tuberosity of the calcaneum was present (8 years). The olecranon was absent (9 years). The outline of the trochlea was visible (9 years). Bone age: 9 years.

The cranium showed a slight increase of density in the anterior and middle fossa, effacement of sphenoid sinus, and an articular calcium band. The roentgenograms are shown in Figures 11, 12 and 13.

INTERESTING PECULIARITIES CONCERNING THESE CASES

1) The very discrete bone lesions, appearing at first glance to be similar to those in Kurzrok's (3) case.
2) The advanced bone age and all the other features pertaining to the syndrome, including the blue sclerae (as in the cases of Nichols (4) and Ubillús (5)). In the literature, as a great number of observations were made only after growth had been completed, the advancement of the bone age could not be observed by all authors; nevertheless this fact has been pointed out in many cases (Albright (6), Hirsch (7), Ubillús (5) and others).
3) The young chronologic age. Reviewing the literature, we noticed that our patients were observed at a much younger age than those of other authors, particularly in Case 1, first studied at the age of 11 months. In Case 2 the patient was observed at the age of $5\frac{1}{2}$ years. One patient of Braid's (8) was studied when 3 years old, and one of Albright's (9), when $3\frac{1}{2}$ years old.
4) Tall stature. Both girls were of a markedly superior height for their ages in relation to the normal values measured in Brazil (Case 1, 84 cm. instead of 74 cm.; and Case 2, 114.7 cm. instead of 106 cm.).
5) Both girls showed fine mental development, distinctly superior for their age. In the younger we noticed a certain nervousness, and in the older, an exaggerated shyness. Observations made by other authors pointed out, on the contrary, a mental retardation.
6) In both girls hormone assays (gonadotropins, estrogens and 17-ketosteroids) gave normal values.
7) In both girls there was an increase of the serum phosphatase and a

slight increase of the phosphorus; calcium, sodium and potassium showed normal values; and cholesterol was increased.

8) Both girls showed a tendency towards a macrocytic anemia (more accentuated in the older girl) and an eosinophilia and lymphocytosis.
9) In Case 1, the girl's mother suffered during the first months of the pregnancy from an intense macrocytic anemia. However, her daughter was not anemic, although manifesting a macrocytic tendency.
10) In Case 2, the girl had a slight macrocytic anemia. We do not possess any hematologic data on the mother.
11) The mothers of both girls presented a certain tendency towards precocious puberty (10 and 11 years); so did the grandmother of one of them ($10\frac{1}{2}$ years).
12) The mothers of both girls also had areas of cutaneous pigmentation, although much slighter. Mondor (10) observed a cutaneous pigmentation in his patient's grandmother; Albright (11), in a son; Damiens (12), in a brother and an aunt. Laserre (13) studied a similar bone disease in his patient's father.

COMMENT

Items 9 and 10 may suggest a possible participation of more than just one sector of the mesenchyma, and item 12, a genetic origin of the syndrome. It is quite logical to consider the mothers' skin blemishes and their tendency towards a precocious puberty as a possible frustrated form of the disease.

The features of Albright's syndrome can be associated and dissociated in several ways:

a) Albright's syndrome, complete.
b) Albright's syndrome, with only the bone lesions (Jaffe-Lichtenstein type, (14)).
c) Albright's syndrome, presenting all the features except the precocious puberty, as is usual in boys; and even in girls, as in Hernberg and Edgren's case (15)).
d) Albright's syndrome, with all the features except the bone lesions (Kurzrok (3); or with some very slight bone lesions, as in our 2 cases).
e) A possible Albright's syndrome, presenting only a cutaneous pigmentation, as in the cases cited in item 12, sometimes with a tendency towards precocious puberty, as in the case of our patients' mothers.

The occurrence of these features, sometimes isolated and sometimes associated, either of embryogenetic or neurogenetic origin, suggests that the centers of these disturbances are in one general vicinity, and are affected now singly, now all together.

SUMMARY

The author reports 2 cases of Albright's syndrome observed in Brazil. Both were girls, one 15 months old, the other 5½ years old. Both showed very early precocious puberty, one first menstruating at the age of 7 months, and the other at the age of 14 months. Both presented extensive cutaneous pigmentations, blue sclerae, advanced bone age, but only very discrete bone lesions. In both there were normal values for urinary gonadotropins, estrogens and 17-ketosteroids; a normal serum calcium; a slightly increased phosphorus; and an increased phosphatase and cholesterol. In both girls the red blood cells showed a macrocytic tendency and one girl also had a slight anemia. The mother of one of them, while pregnant, had a serious anemia with a macrocytic tendency, but her daughter had a normal red blood count. Both girls had lymphocytosis and eosinophilia.

The mothers of both girls presented also a cutaneous pigmentation of the same type as that of their daughters, but of a much lesser degree; and both mothers had a very early first menstruation (at 10 and 11 years, respectively).

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ABSORPTION OF STEROIDS FROM SUBCUTANEOUSLY IMPLANTED TABLETS OF THE PURE HORMONE AND OF THE HORMONE MIXED WITH CHOLESTEROL

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INTRODUCTION

THE comparative rate of absorption of steroid hormones and their esters from subcutaneously implanted tablets has been studied by different observers (1–5). Lipschutz and Vargas (6) have calculated absorption per square millimeter of the tablet. Most important work on the laws governing absorption from tablets has been done by Folley and his associates (7–10).

Tablets prepared by mixing cholesterol with various substances have been in use for a long time (11–13), and great diminution of the absorption rate has been found (12–14). The degree of this diminution and the laws to which it is subject have apparently not been under discussion so far; but the following statements can be made. Whereas cholesterol is not absorbed from tablets of pure cholesterol (15) it is absorbed from hormone-cholesterol tablets; this is shown by the fact that the concentration of the steroid hormone in the hormone-cholesterol tablet does not diminish as it should if absorption is selective (14, 16). One must then suppose that some change in the physical condition of cholesterol is effected through the contact with the steroid hormone. It can be shown that something similar occurs also with the steroid hormone, but in the opposite direction. When using tablets containing 60 per cent of cholesterol and 40 per cent of progesterone, one would suppose that absorption of progesterone would drop two and one-half times compared to tablets of pure progesterone, should absorption per square millimeter remain unchanged. This is not the case. Absorption of progesterone from tablets containing 40 per cent of this steroid drops much more; absorption is about 25 micrograms or less per square millimeter (13) instead of more than 200 to 300 micrograms from similar tablets of pure progesterone, *i.e.*, absorption drops probably ten times instead of two and one-half times. In other words, absorption of progesterone per square millimeter

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of this steroid diminishes greatly when the steroid is mixed with cholesterol.

In the present work, absorption per square millimeter of tablets of pure steroids and of steroids mixed with cholesterol has been studied for different steroids and some of their esters. It was thought that the findings would be both of theoretical and of clinical use.

METHODS

The tablets were used in experiments in which the tumorigenic and antitumorigenic actions of steroid hormones were studied in guinea pigs in this Department by Lip-

TABLE 1. ABSORPTION OF STEROID HORMONES FROM SUBCUTANEOUSLY IMPLANTED TABLETS IN GUINEA-PIGS

Steroid	Tablet or fraction hereof	Number of experiments	Duration of experiments, days	Absorption per animal per day, micrograms	Absorption per day and per sq. mm. of tablet, micrograms
Testosterone*	¼	9	43–44	276.4 ± 7.1	9.1 ± 0.7
Testosterone*	½	5	44	501.8 ± 13.9	9.2 ± 0.6
Testosterone propionate	1	8	90	279.4 ± 6.6	4.3(3.6)** ± 0.1
Methyltestosterone	½	9	92	133.0 ± 9.1	3.5 ± 0.3
Methyltestosterone	1	4	92	316.5 ± 22.6	4.9 ± 0.2
Ethyltestosterone	1	10	91–92	186.6 ± 6.3	2.9 ± 0.1
Vinyltestosterone	1	8	91–94	354.5 ± 13.3	5.5 ± 0.2
Ethinyltestosterone	1	203	89–93	25.7 ± 0.6	0.4 ± 0.01
Dihydrotestosterone	½	6	90	62.2 ± 8.4	1.6 ± 0.1
Dihydrotestosterone	1	6	90	93.3 ± 8.9	1.4 ± 0.2
Methyldihydrotestosterone	½	8	91–92	119.6 ± 12.5	3.2 ± 0.4
Methyldihydrotestosterone	1	16	92	176.5 ± 8.9	2.7 ± 0.1
Alpha-estradiol	½	70	72–76	69.5 ± 1.5	1.4 ± 0.03
Estradiol caprylate	1	19	72–76	16.3 ± 0.7	0.3(0.2)** ± 001

* Tablets of testosterone prepared by Ciba, Basel, were larger than those of the remaining steroids. The diameter was 7 mm. and the thickness, 0.9 mm. The surface area was 96.7 sq. mm.; that of half a tablet, 54.6 sq. mm. and of a quarter of a tablet, 30.5 sq. mm. The remaining substances were absorbed from tablets with a surface area of 64.8 sq. mm. for an entire tablet, and 37.9 sq. mm. for half a tablet (*see* Methods).

** Calculated for the free hormone.

schutz and his associates for many years. The duration of the experiments was usually ninety days, with but few exceptions. The tablets were prepared with a hand machine, with one exception (testosterone) as noted in Table 1. The tablets were cylindrical, the diameter was 5.5 mm., the thickness about 1 mm., and the weight about 30 mg. The surface was calculated for a uniform height of 1 mm. (64.8 sq. mm.). Before implantation, tablets were dried in vacuo with $CaCl_2$; implantation was always in a pocket beneath the skin. At necropsy the tablets were freed from the surrounding tissues, cleaned with water and dried.

When preparing the mixture, cholesterol and the steroid hormone were dissolved in ether which was evaporated at 60° C. The residue was triturated, compressed to tablets, dried and weighed.

The following errors have to be considered:

1. The difference between the original weight of the tablet and the weight at the end of the experiment was taken as the "total absorption." This figure is only approximate since substances from the outside enter into the tablets (7a, 10). With hexestrol tablets the percentage error from this cause may be considerable, but it amounts to about only 15 per cent at 77–105 days (17). As already mentioned, our experiments, with but few exceptions, were of no less than ninety days' duration.

2. Absorption per day was calculated by dividing total absorption by the number of days. This procedure gives only approximate figures, as absorption per day diminishes with the time (2, 8, 12), most probably due to the diminution of surface during the experiment. Such an error was of minor importance in our work, in which experiments lasted in general no more than ninety days, except for the case of pure testosterone which is absorbed more rapidly. All the cases in which tablets became greatly reduced were omitted so as to avoid too great errors.

3. Thickness of tablets was variable from the beginning, whereas all our calculations were on the basis of a uniform surface value. However, even with tablets 1.5 mm. instead of 1 mm. thick, the error would have been only 13 per cent—an error which was indeed never reached.

4. Not only entire tablets but also "half" a tablet, and with one substance even a "quarter" of a tablet, were used in some experiments. Since separation of a tablet into parts was never exact, a considerable error was seemingly introduced. As will be seen from Table 1 the error may reach 30 per cent and even 40 per cent (*cf.* testosterone and methyltestosterone).

5. Since compression was by hand it would seem that an uncontrollable error was introduced. Nevertheless, it has been found that the absorption rate, for instance of hexestrol, was independent of the pressure over a considerably wide range (9).

RESULTS

As will be seen from Tables 1 and 2, the standard deviation was very small notwithstanding the errors enumerated, thanks to the great number of tablets available—in general, no less than 10 for each steroid.

As had to be expected on the basis of the well known work of so many observers, absorption of testosterone propionate per sq. mm. was only half that of the free hormone. All C_{17} derivatives of testosterone behaved similarly to the ester.

Most remarkable was the slow absorption per sq. mm. of ethinyltestosterone compared to testosterone; there was a twenty-three fold difference.

The figures as given in the last column of Table 1 may serve for calculating tentatively the surface necessary for procuring absorption of a desired quantity of the respective steroid. It is, indeed, impossible to say whether these figures are valid also for humans though this would seem probable.

Comparative absorption from tablets of pure steroid hormones and from mixtures of these with cholesterol is given in Table 2 for 5 steroids.

As expected, absorption *per square millimeter of tablet* dropped when the mixture was used. In our tablets containing the mixture, the surface

TABLE 2. COMPARATIVE ABSORPTION FROM TABLETS OF PURE STEROID HORMONES AND THEIR MIXTURES WITH CHOLESTEROL

Composition of the tablet	Number of experiments	Duration of experiments, days	Total absorption of the group per day, micrograms	Total surface of the group, sq. mm.	Absorbed per day and per sq. mm. *of tablet* (*actual* absorption), micrograms	Absorbed per day and per sq. mm. *of steroid* hormone (*calculated* absorption), micrograms	Relation of absorption from pure and from mixed tablets *per sq. mm. of steroid hormone*
Testosterone, pure	14	43–44	4,997	548	9.1±0.6	9.1	1:0.15
Testosterone, 40%	38	90	1,164	2,193	0.5±0.02	*1.3	
Ethyltestosterone, pure	10	92	1,866	648	2.9±0.1	2.9	1:0.5
Ethyltestosterone, 40%	16	91–92	606	1,037	0.6±0.1	*1.5	
Vinyltestosterone, pure	8	91–94	2,836	518	5.5±0.4	5.5	1:0.12
Vinyltestosterone, 40%	34	91–94	541	1,988	0.3±0.01	*0.7	
Dihydrotestosterone, pure	12	90	933	616	1.5±0.1	1.5	1:0.38
Dihydrotestosterone, 40%	10	91–92	119	514	0.2±0.02	*0.6	
Progesterone, pure	28	90	5,694	1,814	3.1±0.1	3.1	1:0.22
Progesterone, 40%	26	90	321	1,130	0.3±0.02	*0.7	
Diethylstilbestrol, pure	27	49–127	5,037	1,750	2.9±0.1	2.9	1:0.11
Diethylstilbestrol, 40%	29	90–93	249	1,879	0.1±0.01	*0.3	

* Calculated by multiplying the figure in column 6 by 2.5.

occupied by the steroid hormone was 40 per cent of the total surface. One would expect that absorption would diminish in the same proportion; but, as seen from column 6 in Table 2, absorption diminished eighteenfold in the testosterone mixture and more than tenfold in the progesterone mixture. Consequently, absorption *per square millimeter of the steroid hormone* was considerably diminished (last two columns of Table 2).

Thus, when a steroid hormone is absorbed from a mixture with cholesterol, absorption diminishes not only on account of the reduced surface of the hormone but also because absorption is in some way counteracted by cholesterol. On the contrary, absorption of the latter is enhanced by the steroid hormone (14). The slowing down of absorption of steroid hormones from tablets in which the hormones are mixed with cholesterol

can be compared to older observations of the Laqueur group who showed that the activity of steroid hormones absorbed from oily solutions was enhanced when fatty acids were added.

SUMMARY

Absorption of different steroid hormones per square millimeter of a subcutaneously implanted tablet has been calculated.

In the guinea pig, absorption per square millimeter per day was about 9 micrograms for testosterone, 3 micrograms for progesterone and 1.4 micrograms for α-estradiol.

Absorption of C_{17} derivatives of testosterone was about two to three times less, and absorption of ethinyltestosterone was about twenty-three times less than absorption of testosterone.

Absorption from tablets containing 40 per cent of the steroid hormone and 60 per cent of cholesterol dropped to one fifth and even to one twentieth of that of the pure hormone tablets, although a diminution of only two and one half times would be expected according to the reduction of the surface of the steroid hormone in the mixture.

Cholesterol in some way counteracts absorption of steroid hormones.

Acknowledgment

Thanks for a generous supply of steroids are due to Dr. Karl Miescher of Ciba Pharmaceutical Products, Basel, Switzerland; to Dr. E. Oppenheimer of Ciba Pharmaceutical Products, Summit, N. J.; and to Dr. M. Tausk of Organon, Oss, Holland.

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Letter to the Editor

DESOXYCORTICOSTERONE ACETATE IN THE TREATMENT OF INSULIN RESISTANCE

To the Editor:

ZIMMERMAN and his co-workers reported (*Proc. Soc. Exper. Biol. & Med.* **73**: 81–92, 1950)[1] that insulin insensitive diabetic patients were rendered insulin sensitive by the administration of desoxycorticosterone acetate (DOCA). Their report suggested the possible use of DOCA in the treatment of insulin resistance. The results of such a therapeutic trial in a 64-year-old female diabetic with moderately severe insulin resistance[2] are shown in the table.

Date, 1950	Blood sugar range, mg./100 cc.	Urinary 11-oxysteroids, mg./24 hrs.	Urinary 17-ketosteroids, mg./24 hrs.	Daily urine sugar, Gm.	Total daily insulin dose, units	DOCA dose, mg.
3/29	186–372				240	
3/30	206–341				175	
3/31	338–400				530	
4/1	146–372				220	
4/2	220–417				555	
4/3	78–318	1.1	2.6	44	505	
4/4	88–280	1.4		10	340	
4/5	273–351				455	10
4/6	238–420				530	10
4/7	193–314			103	755	10
4/8	187–364			88	955	10
4/9	214–364			98	805	10
4/10	234–312	1.1		79	880	10
4/11	83–208			37	465	
4/12	286–320			29	505	
4/13	304			87	505	
4/14	215–346	0.9		15	505	
4/15	143–320				505	

Because the increase in insulin requirements up to a maximum of 955

[1] Read at the Annual Meeting of the Association for the Study of Internal Secretions, San Francisco, California, June 24, 1950.

[2] The patient did not show any signs of insulin allergy.

units on April 8 coincided with DOCA therapy, the administration of DOCA was terminated on the sixth day. It appeared that DOCA, instead of increasing insulin sensitivity, exhibited a diabetogenic effect either directly or by exaggerating or stimulating the action of contra-insular substances already present. The 10 mg. dose level was that advocated by Zimmerman *et al.* and was sufficient to reduce the hematocrit from 44 per cent to 36 per cent. Hyperadrenocorticism was not the pathogenic mechanism in this patient, as evidenced by her normal corticoid and subnormal 17-ketosteroid excretion. Despite this unfavorable report, further clinical trials of DOCA seem warranted in cases of insulin resistance particularly when hyperactivity of the adrenal cortex can be demonstrated.

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Acknowledgment. The author wishes to thank Dr. William H. Perloff, Chief of the Endocrine Clinic, Philadelphia General Hospital, for the supply of DOCA and for the performance of the bio-assays.

The Association for the Study of Internal Secretions

THE 1951 ANNUAL MEETING

The Thirty-third Annual Meeting of the Association for the Study of Internal Secretions will be held at the Chalfonte-Haddon Hall Hotel, Atlantic City, New Jersey. The Scientific Sessions have been extended to three days, Thursday, Friday, and Saturday, June 7-8-9.

The Local Chairman of Arrangements is Dr. Matthew Molitch.

Due to the advance in the date of our meeting, Chalfonte-Haddon Hall Hotel will be unable to accommodate all of our members by reason of a previous commitment. The Colton Manor, on Pennsylvania Avenue near Haddon Hall, is an excellent hotel, which has been recently refurnished, and is holding one hundred rooms for our members on the "first come, first served" basis. The Hotel Strand, at Pennsylvania Avenue and the Boardwalk, has also promised to supply a limited number of rooms. It is important that reservations be made immediately if you are to avoid disappointment.

All Scientific Sessions will be held in the Chalfonte-Haddon Hall Hotel. The rooms, in which the session will be held, will be announced in the program and on the hotel bulletin board. The Annual Dinner is scheduled for Friday, June 8, at 7:30 P.M. in the Rutland Room, preceded by cocktails at 6:30 P.M. in the adjoining Benjamin West Room.

Those wishing to present papers, which will be limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. Jane Russell, School of Medicine, Emory University, Atlanta, Georgia, not later than *March 1, 1951. It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and journals of the Association.* The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. References, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.

2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each non-member author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of non-members who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *i.e.*, M.D., of each author should be given after his name.
   Line 3. Institution of origin and city in which institution is located.
3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter-perfect, since there will be no opportunity for proof reading by authors.

THE 1951 AWARDS AND FELLOWSHIPS

Fellowships

THE AYERST McKENNA AND HARRISON FELLOWSHIP

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected for the Fellowship in 1949, and the 1950 Fellowship was awarded to Dr. Lawrence E. Shulman.

THE SCHERING FELLOWSHIP IN ENDOCRINOLOGY

The Schering Fellowship in Endocrinology was established in 1949 and the first recipient was Dr. D. Laurence Wilson, who also received the 1950 Fellowship.

Association Fellowships are designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $2,500.00, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study,

indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

Awards

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb & Sons Award of $1,000.00 was established in 1929, and was given first in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr E. A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori; in 1948 to Dr. Fuller Albright; in 1949 to Dr. Herbert M. Evans; and in 1950 to Dr. C. N. H. Long. In 1943 no award was given. A special committee of five members of the Association selects the recipient from among investigators in the United States or Canada, on the basis of outstanding contributions to endocrinology.

THE CIBA AWARD

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than thirty-five years of age in the field of clinical or preclinical endocrinology was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Helier; in 1949 to Dr. George Sayers; and in 1950 to Dr. Oscar M. Hechter. The Award is for $1,200.00. If within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $1,800.00.

NOMINATIONS

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in, endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on special application forms which may be obtained from the *Secretary, Dr. Henry H. Turner,* 1200 North Walker Street, Oklahoma City 3, Oklahoma, and returned to him *not later than March 15, 1951.*

The American Goiter Association

THE 1951 ANNUAL MEETING

The next Annual Meeting of the American Goiter Association will be held in Columbus, Ohio, May 24, 25 and 26, 1951, at the Deshler Wallick Hotel.

VAN METER PRIZE AWARD FOR 1951

THE American Goiter Association again offers the Van Meter Prize Award of three hundred dollars, and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Columbus, Ohio, May 24, 25, 26, 1951, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy in duplicate sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, *not later than March 1, 1951.* The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.

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STERILITY AWARD

The American Society for the Study of Sterility is offering an Annual Award of $1,000 known as the Ortho Award for an essay on the result of some clinical or laboratory research pertinent to the field of sterility. Competition is open to those who are in clinical practice as well as to individuals whose work is restricted to research in basic fields or full-time teaching positions.

Full particulars concerning the competition for the 1951 Award may be obtained by addressing the Secretary, Walter W. Williams, M.D., 20 Magnolia Terrace, Springfield 3, Massachusetts.